PB81-117368

Ambient Water Quality Criteria for Cadmium

(U.S.) Environmental Protection Agency
Washington, DC

Oct 80

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-025
October 1980

PB81-117368

EPA

Ambient Water Quality Criteria for Cadmium

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NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO.

2.

3. RECIPIENT'S ACCESSION NO.
PB81 117368

4. TITLE AND SUBTITLE
Ambient Water Quality Criteria for:
Cadmium

5. REPORT DATE
October, 1980

6. PERFORMING ORGANIZATION CODE
NTISEPAOWP

7. AUTHOR(S)
Environmental Criteria and Assessment Office

8. PERFORMING ORGANIZATION REPORT NO.
EPA-440/5-80-025

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Office of Water Regulations and Standards
Criteria and Standards Division
U.S. Environmental Protection Agency
Washington, D.C. 20460

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
Same as box 9

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES
Supersedes draft document PB 292 423

16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Cadmium. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT
For Public Release

19. SECURITY CLASS *(This Report)*
Unclassified

20. SECURITY CLASS *(This page)*
Unclassified

21. NO. OF PAGES

22. PRICE

EPA Form 2220-1 (9-73)

AMBIENT WATER QUALITY CRITERIA FOR
CADMIUM

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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ACKNOWLEDGEMENTS

Aquatic Life Toxicology

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CRITERIA DOCUMENT

CADMIUM

CRITERIA

Aquatic Life

For total recoverable cadmium the criterion (in µg/l) to protect freshwater aquatic life as derived using the Guidelines is the numerical value given by $e^{(1.05\ (\ln(\text{hardness}))-8.53)}$ as a 24-hour average and the concentration (in µg/l) should not exceed the numerical value given by $e^{(1.05\ (\ln(\text{hardness}))-3.73)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the criteria are 0.012, 0.025, and 0.051 µg/l, respectively, and the concentration of total recoverable cadmium should not exceed 1.5, 3.0, and 6.3 µg/l, respectively, at any time.

For total recoverable cadmium the criterion to protect saltwater aquatic life as derived using the Guidelines is 4.5 µg/l as a 24-hour average and the concentration should not exceed 59 µg/l at any time.

Human Health

The ambient water quality criterion for cadmium is recommended to be identical to the existing water standard which is 10 µg/l. Analysis of the toxic effects data resulted in a calculated level which is protective of human health against the ingestion of contaminated water and contaminated aquatic organisms. The calculated value is comparable to the present standard. For this reason a selective criterion based on exposure solely from consumption of 6.5 grams of aquatic organisms was not derived.

INTRODUCTION

Cadmium, atomic weight 112.40, is a soft silver white metal with a melting point of 321°C and a boiling point of 765°C (Windholz, 1976). It is used in electroplating, paint and pigment manufacture and as a stabilizer in plastics manufacture (Fulkerson and Goeller, 1973). The solubility of cadmium compounds in water depends on the nature of the compounds and on water quality. Compared to other heavy metals, cadmium is relatively mobile in the aquatic environment and may be transported in solution as either hydrated cations or as organic or inorganic complexes (U.S. EPA, 1979). Cadmium ion is precipitated from solution by carbonate, as hydroxide and sulfide ions (Baes, 1973) and forms soluble complexes with other anions (Samuelson, 1963).

Cadmium reaches waterways as fallout from air and in effluents from pigments, plastics, alloys and other manufacturing operations as well as from municipal effluents. Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides (Watson, 1973), all of which tend to remove it from the water column by precipitation. In polluted waters complexing with organic materials is the most important factor in determining the aquatic fate and transport of cadmium. Sorption processes account for removal of dissolved cadmium to bed sediments and are increasingly effective as pH increases (U.S. EPA, 1979).

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Aquatic Life Toxicology*

INTRODUCTION

In natural freshwaters cadmium sometimes occurs at extremely low concentrations (less than 0.01 µg/l), but in environments impacted by man, cadmium concentrations can be several micrograms per liter or greater. Predicting the impact of cadmium on aquatic organisms may be complicated by the variety of possible chemical forms of cadmium, which may display different levels of toxicity and bioaccumulation. In addition synergism and antagonism may occur.

However, a first-approximation of the aqueous chemistry of cadmium can be obtained from the pH, carbonate alkalinity and concentrations of calcium, magnesium, and cadmium. Complex formation by common anions, such as chloride and sulfate, in well-oxygenated fresh water is relatively weak. Only when concentrations of these components become high (e.g., 10^{-2}M) is approximately half of the cadmium complexed. Thus in waters with low total organic carbon and low concentrations of other less prevalent but relatively strong complexing agents, such as aminopolycarboxylic acids, the free cadmium ion should be the predominant dissolved species.

Precipitation of cadmium hydroxide should occur only when the pH reaches 10 or 11 with relatively high cadmium concentrations. Furthermore, at concentrations of approximately 1 µg/l and below cadmium carbonate probably will not precipitate, provided that the approximate limits of pH 8.5 and total carbonate of 10^{-2}M - usually near the maximum for natural waters - are not exceeded.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

In saltwater systems with typical salinity, the number of probable cadmium species is reduced to a few because cadmium chloride complexes probably predominate.

Of the analytical measurements currently available, a water quality criterion for cadmium is probably best stated in terms of total recoverable cadmium, because of the variety of forms that can exist in bodies of water and the various chemical and toxicological properties of these forms. The forms of cadmium that are commonly found in bodies of water and are not measured by the total recoverable procedure, such as the cadmium that is a part of minerals, clays and sand, probably are forms that are less toxic to aquatic life and will not be converted to the more toxic forms very readily under natural conditions. On the other hand, forms of cadmium that are commonly found in bodies of water and are measured by the total recoverable procedure, such as the free ion, and the hydroxide, carbonate, and sulfate salts, probably are forms that are more toxic to aquatic life or can be converted to the more toxic forms under natural conditions.

Because the criterion is derived on the basis of tests conducted on soluble inorganic salts of cadmium, the total and total recoverable concentrations in the tests will probably be about the same, and a variety of analytical procedures will produce about the same results. Except as noted, all concentrations reported herein are expected to be essentially equivalent to total recoverable cadmium concentrations. All concentrations are expressed as cadmium, not as the compound tested.

EFFECTS

Acute Toxicity

Freshwater acute toxicity values for cadmium range from 1 to 73,500 µg/l for fish species and from 3.5 to 28,000 µg/l for invertebrate species (Table

1). A reduction in toxicity associated with increased hardness is evident for several fish and invertebrate species. Carrol, et al. (1979) verified that the calcium reduces the acute toxicity of cadmium. In most natural waters, calcium and magnesium are both present, with calcium being somewhat more abundant. Giesy, et al. (1977) found that equilibrium associations of cadmium with dissolved organics changed its toxicity to daphnids substantially but little to fish. No consistent relationship of toxicity to organic particle size was demonstrated.

Among invertebrates, cladocerans were the most sensitive species, and mayflies and stoneflies were the most resistant. However, insects and other invertebrates are more sensitive during molting, which usually does not occur among most individuals during tests lasting 96 hours or less.

Among fish species, salmonids appear to be the most vulnerable to cadmium (Tables 1 and 6). Few data are available comparing the toxicity of cadmium to salmonids in hard and soft water, although those of Carrol, et al. (1979) and Davies (1976) agree genrerally with the data for warm water fish. A comparison of Davies' data requires use of the 1.75 µg/l LC_{50} from Table 1 (hardness 31 mg/l) and the 96-hour LC_{20} of 20 µg/l from Table 6 (hardness 326 mg/l).

A relatively large unexplained difference exists between toxicity values from Rehwoldt, et al. (1972) and Hughes (1973) for striped bass tested at similar hardnesses.

An exponential equation was used to describe the observed relationship of the acute toxicity of cadmium to hardness in fresh water. For eight individual species a least squares regression was performed on the natural logarithms of the acute values and the natural logarithms of hardness (Table 1). Only two or three data points were available for most species, and for several the hardnesses were not well distributed. In spite of these problems seven of the eight slopes were between 0.48 and 1.56 with an arithmetic mean of 1.05. The other slope was slightly negative and was not used.

The arithmetic mean slope (1.05) was used with the geometric mean toxicity value and hardness for each species to obtain a logarithmic intercept for each of the 29 freshwater species for which acute values are available for cadmium. The species mean acute intercept, calculated as the exponential of the logarithmic intercept, was used to compare the relative acute sensitivities (Table 3). A freshwater Final Acute Intercept of 0.024 µg/l was obtained for cadmium using the Species Mean Acute Intercepts listed in Table 3 and the calculation procedures described in the Guidelines. Thus the Final Acute Equation is $e^{(1.05[\ln(\text{hardness})]-3.73)}$.

Acute toxicity data for cadmium are available for 31 species of saltwater fish and invertebrate species (Table 1). The invertebrates are represented by 26 species with acute values ranging from 15.5 µg/l for the mysid shrimp (Nimmo, et al. 1977a) to 46,600 for the adult fiddler crab (O'Hara, 1973). The acute values for adult saltwater polychaetes range from 7,500 µg/l for _Capitella capitata_ to 12,000 µg/l for _Neanthes arenaceodentata_ (Reish, et al. 1976), and the larvae of _Capitella capitata_ are 35 times more sensitive than the adults. Saltwater molluscs have acute values from 850 µg/l for the soft-shelled clam (Eisler, 1977) to 35,000 µg/l for the mud snail (Eisler and Hennekey, 1977).

Frank and Robertson (1979) reported that the acute toxicity to juvenile blue crabs was related to salinity. The 96-hour acute toxicities were 320, 4,700, and 11,600 µg/l at salinities of 1, 15, and 35 g/kg, respectively. O'Hara (1973) investigated the effect of temperature and salinity on cadmium toxicity with the fiddler crab and did not find a significant effect of salinity. Acute toxicities at 20°C were 32,300, 46,600, and 37,000 at 10, 20, and 30 g/kg salinity. Increasing the temperature from 20° to 30°C increases toxicity at all salinities tested.

The calanoid copepods Acartia tonsa and Acartia clausi were an order of magnitude more sensitive than other copepods with species acute values of 169 µg/l and 144 µg/l, respectively. Acute toxicity values for the mysid shrimp, Mysidopsis bahia, were 15.5 µg/l at 25°C to 28°C and 10 to 77 g/kg salinity (Nimmo, et al. 1977a), and 110 µg/l at 21°C and 30 g/kg salinity (U.S. EPA, 1980). M. bigelow had a 96-hour LC_{50} and 135 µg/l which was similar to M. bahia (U.S. EPA, 1980). Lobster larvae were acutely sensitive to cadmium with a 96-hour LC_{50} of 78 µg/l.

The saltwater of fish species were generally more resistant to cadmium with acute values ranging from 577 for the larvae of Atlantic silversides (U.S. EPA, 1980) to 114,000 µg/l for juvenile mummichog (Voyer, 1975). In a study of the interaction of dissolved oxygen salinity on the acute toxicity of cadmium to the mummichog, Voyer (1975) found similar toxicities at salinities of 10 and 20 g/kg but a doubling of the sensitivity at 30 g/kg. Resistance of mummichogs to acute cadmium poisoning was not influenced by reductions in dissolved oxygen levels to 4 mg/l.

The saltwater Final Acute Value for cadmium, derived from the Species Mean Acute Values listed in Table 3 using the calculation procedures described in the Guidelines, 58.6 µg/l.

Chronic Toxicity

The range in freshwater chronic toxicity values (0.15 to 50 µg/l) is much less than the range in acute toxicity values. Daphnia magna is the most sensitive species tested, and Bertram and Hart (1979) found chronic toxicity to Daphnia pulex at 1 µg/l (Table 6). A 200-hour LC_{10} value of

0.7 µg/l for rainbow trout was obtained by Chapman (1978) and probably would be close to the result of an early life stage test because of the extent to which various life stages were investigated (Table 6). Other salmonids and many invertebrates are also quite sensitive, with effects having been observed at 5 µg/l or less (Table 6). These organisms include decomposers (Giesy, 1978), crayfish (Thorp, et al. 1979), copepods and annelids (Giesy, et al. 1979), midges (Anderson, et al. 1980) and mayflies (Spehar, et al. 1978).

The acute-chronic ratios for all freshwater species are surprisingly similar considering the variety of organisms, hardnesses, and chronic toxicities involved. The geometric mean acute-chronic ratio for Daphnia magna is 122, and that for all four freshwater organisms is 231. The acute-chronic ratio appears to be independent of hardness, but more sensitive species appear to have a lower ratio than less sensitive ones. Thus 122 will be used as the Final Acute-Chronic Ratio, and the Freshwater Final Chronic Intercept of 0.000197 µg/l is obtained by dividing the Final Acute Intercept of 0.024 µg/l by 122. Also, if the acute-chronic ratio is independent of hardness, the chronic slope must be equal to the mean acute slope of 1.05. Thus the Freshwater Final Chronic Equation (Table 3) is $e^{(1.05[\ln(\text{hardness})]-8.53)}$.

Some data are available concerning the effect of hardness on chronic toxicity of cadmium. If a chronic slope is calculated using the technique described earlier for calculating the acute slope, the four chronic tests with Daphnia magna produce a slope of 0.35. If only the three tests of Chapman (Manuscript) are used, the slope is 0.79. The slope calculated from all four chronic tests with brook trout is 1.01. Thus it appears that hardness affects the acute and the chronic toxicity of cadmium similarly.

Using the slope of 1.05, species mean chronic intercepts were calculated for all 13 species with which chronic tests have been conducted on cadmium. These chronic intercepts range from 0.359 µg/l for the walleye to 0.00248 for Daphnia magna (Table 2). Even though four salmonids and only one invertebrate are on the list, the range of sensitivities is rather large.

Two chronic toxicity studies have been conducted with the saltwater invertebrate, Mysidopsis bahia (Table 2). Nimmo, et al. (1977a) conducted a 23-day life cycle test at 20° to 28°C and 15 to 23 g/kg salinity. Decreased survival occurred at 10.6 µg/l, whereas a 48-hour delay in brood formation, 24-hour delay in brood release, and a 57 percent decrease in the number of young per female resulted at 6.4 µg/l. No adverse effects were detected at 4.8 µg/l. The chronic toxicity limits, therefore, are 4.8 and 6.4 µg/l with a chronic value of 5.5 µg/l. The 96-hour LC_{50} was 15.5 µg/l resulting in an acute-chronic ratio of 2.8.

A second life cycle study was conducted with cadmium and Mysidopsis bahia under different environmental conditions (U.S. EPA, 1980). Experimental conditions included constant temperature (21°C) and salinity (30 g/kg). Complete mortality occurred after 28 days' exposure at 25 µg/l. At 11.5 µg/l a series of morphological aberrations occurred at the onset of sexual maturity. External genitalia in males were aberrant, females failed to develop brood pouches, and both sexes developed a carapace malformation that prohibited molting after the release of the initial brood. Although initial reproduction at this concentration was successful, successive broods could not be borne because molting resulted in death. No malformations or effects on initial or successive reproductive processes were noted in the controls or at 5.5 µg/l. The chronic limits for this study are 5.5 and 11.5 with a chronic value of 8.0 µg/l. The LC_{50} at 21°C and 30 g/kg salinity was 110 µg/l which results in an acute-chronic ratio of 14 from this study.

These two studies showed excellent agreement between the chronic values but considerable divergence between the acute values and acute-chronic ratios. Several studies have demonstrated an increase in acute toxicity of cadmium with decreasing salinity and increasing temperature (Table 6). The observed differences in acute toxicity to the mysids might be explained on this basis. Nimmo, et al. (1977a) conducted their acute test at 25° to 28°C and 10 to 17 g/kg salinity, whereas the other test (U.S. EPA, 1980) was performed at 21°C and 30 g/kg salinity.

Because only one chronic test has been conducted with a saltwater species and the resulting acute-chronic ratio is so different from those found with freshwater species, it would be inappropriate to use the geometric mean of all available acute-chronic ratios to calculate the saltwater Final Chronic Value. Therefore, no Final Acute-Chronic Ratio and no Final Chronic Value can be calculated for saltwater species.

Plant Effects

Growth reduction was the major toxic effect observed with freshwater aquatic plants (Table 4), and several values are in the range of concentrations causing chronic effects in animals. The influence that plant growth media may have had on the toxicity studies is unknown but is probably minor, at least in the case of Conway (1978), who used a medium patterned after natural Lake Michigan water. Because the lowest toxicity values for fish and invertebrates species are lower than the values for plants, water quality criteria which protect aquatic animals should also protect aquatic plants.

Plant studies were reported with two species of saltwater phytoplankton (Table 4). Thalassiosira pseudonana and Skeletonema costatum had 96-hour EC_{50} values of 160 and 175 µg/l, respectively, based on growth inhibition. These values are considerably above the chronic values for mysid shrimp and are above the acute values for many saltwater animal species.

Residues

Bioconcentration factors for cadmium in freshwater (Table 5) were highly variable, ranging from 3 for brook trout muscle (Benoit, et al. 1976) to 12,400 in the whole body of mosquitofish (Giesy, et al. 1977). Usually, fish accumulate only small amounts of cadmium in muscle as compared to most other tissues and organs (Benoit, et al. 1976; Sangalang and Freeman, 1979). Also, cadmium residues in fish reach steady-state only after exposure periods greatly exceeding 28 days (Benoit, et al. 1976; Sangalang and Freeman, 1979; Giesy, et al. 1977). Daphnia magna, and presumably other invertebrates of about this size or smaller, often reach steady-state within a few days (Poldoski, 1979). Cadmium accumulated by fish from water is eliminated slowly (Benoit, et al. 1976; Kumada, et al. 1980), but Kumada, et al. (1980) found that cadmium accumulated from food is eliminated much more rapidly.

Mallard ducks are the only native wildlife species whose chronic sensitivity to cadmium has been studied. These birds can be expected to ingest many of the different freshwater plants and animals listed in Table 4. White and Finley (1978a,b) found significant damage occurring at a cadmium concentration of 200 mg/kg in food for 90 days. Division of 200 mg/kg by the geometric mean bioconcentration factor of 766 gives a Final Residue Value of 260 µg/l. This is a concentration which would cause damage to mallard ducks, but no additional data are available.

Among saltwater species, bioconcentration factors for cadmium have been determined for 1 species of alga, 13 species of invertebrates, and 1 species of fish (Table 5). Values range from 22 to 3,160 for whole body and from 5 to 2,040 for muscle. Kerfoot and Jacobs (1976) reported a bioconcentration factor of 670 for the alga Prasinocladus tricornutum. Theede, et al. (1979)

found that the colonial hydroid Laomedea loveni bioconcentrated cadmium 153 times within a 10-day exposure period. The highest bioconcentration factor was reported for the polychaete Ophryotrocha diadema (Klockner, 1979). After 64 days' exposure using the renewal technique, a bioconcentration factor of 3,160 was attained. Tissue residues, however, had not reached steady-state.

Bioconcentration factors for five species of bivalve molluscs range from 83 for the hard shelled clam (Kerfoot and Jacobs, 1976) to 3,650 for the American oyster (Zaroogian and Cheer, 1976). In addition, the range of reported bioconcentration factors is rather large for some individual species. Bioconcentration factors for the oyster include 149 (Eisler, et al. 1972), 677 (Kerfoot and Jacobs, 1976), 1,220 (Schuster and Pringle, 1969), and 3,650 (Zaroogian, 1979). Similarly, two reported studies on bay scallops report bioconcentration factors of 168 (Eisler, et al. 1972) and 2,040 (Pesch and Stewart, 1980), and three studies on the mussel report bioconcentration factors of 113 (George and Coombs, 1977), 306 (Phillips, 1976), and 710 (Janssen and Scholz, 1979). Because bivalve molluscs do not, as a rule, reach steady-state, comparisons between species may be difficult. The length of exposure may be the major determinant in the size of the bioconcentration factor.

Bioconcentration factors for six species of crustaceans range from 22 to 307 for whole body and from 5 to 25 for muscle (Table 5). Nimmo, et al. (1977) reported bioconcentration factors for two species of grass shrimp, Palaemonetes pugio and Palaemonetes vulgaris, of 203 and 307, respectively, for whole body. Vernberg, et al. (1977) reported a factor of 140 for P. pugio at 25°C, while Pesch and Stewart (1980) reported a factor of only 22 for the same species exposed at 10°C, indicating that temperature is probably an important variable.

The commercially important crustaceans, the pink shrimp and lobster, were not effective bioaccumulators of cadmium with factors of 57 for whole body and 25 for muscle, respectively. A single bioconcentration factor of 48 is reported for saltwater fishes (Eisler, et al. 1972) which probably indicates that fish also do not bioconcentrate cadmium effectively.

George and Coombs (1977) studied the importance of metal speciation on cadmium accumulation in the soft tissues of Mytilus edulis. Cadmium complexed as Cd-EDTA, Cd-alginate, Cd-humate, and Cd-pectate (Table 6) was bio concentrated at twice the rate of inorganic cadmium (Table 5).

Although a high degree of variability exists between the bioconcentration factors reported for saltwater organisms, shellfish can accumulate cadmium in tissues to concentrations potentially harmful to man. Zaroogian and Cheer (1976) and Zaroogian (1979) reported BCFs of 2,600 and 3,650, respectively, with oysters after long-term exposures. The emetic threshold of cadmium is 13 to 15 mg/kg for man (Anon., 1950), which results in a Saltwater Final Residue Value of 4.5 μg/l (Table 5).

Miscellaneous

The cumulative mortality resulting from exposure to cadmium for more than 96 hours is clearly evident from the studies of Reish, et al. (1976) on polychaetes; Eisler and Hennekey (1977) on bivalve molluscs, crabs, and starfish; Pesch and Stewart (1980) on scallops, shrimp, crabs; and on mysid shrimp (U.S. EPA, 1980; Nimmo, et al. 1977a). Nimmo, et al. (1977a) in studies with mysid shrimp, Mysidopsis bahia, reported a 96-hour LC_{50} of 15.5 μg/l (Table 1) and a 17-day LC_{50} of 11 μg/l (Table 6) at 25° to 28°C and 15 to 23 g/kg salinity. In another series of studies on this mysid (U.S. EPA, 1980), the 96-hour LC_{50} was 105 μg/l (Table 1), and the 28-day LC_{50} was 16 μg/l (Table 6) at 20°C and 30 g/kg salinity. Comparison of these data leads to the hypothesis that short-term acute toxicity may be strongly influenced by environmental variables, whereas long-term effects, including mortality, are not. This pattern was also reflected in the similarity of reproductive responses of this species (Table 2) tested under dissimilar environmental conditions.

Two studies of chronic exposure are illustrative of the effects of cadmium on growth and fecundity (Table 6). Pesch and Stewart (1980) in a 42-day study of cadmium toxicity to the bay scallop reported that 60 and 120 µg/l reduced growth 42 and 69 percent, respectively, which results in an EC_{50} of about 78 µg/l. D'Agostino and Finney (1974) studied the effects of cadmium on the development and sexual maturation of the copepod *Tigriopus japonicus*. Cadmium inhibited the development of ovigerious females and hence the production of the young at concentrations greater than 44 µg/l. The 96-hour LC_{50} for *T. japonicus* is 5,290 (Table 1). Although the concentration of cadmium in the test solution was not measured, these results do indicate that cadmium can produce long-term cumulative effects on reproduction.

Considerable data exist concerning the effect of salinity and temperature on the acute toxicity of cadmium. Unfortunately the conditions and durations of exposure are so different that adjustment of acute toxicity data for salinity is not possible. Rosenberg and Costlow (1976) studied the synergistic effects of cadmium and salinity combined with constant and cycling temperatures on the larval development of two estuarine crab species. They reported reduction in survival and significant delay in development of the blue crab with decreasing salinity. Three times as much cadmium was required to produce an LC_{50} at 30 than at 10 g/kg salinity. Studies with the mud crab resulted in a similar cadmium-salinity response. In addition, the authors report that cycling temperatures may have a stimulating effect on survival of larvae compared to constant temperatures.

Theede, et al. (1979) investigated the effect of temperature and salinity on the acute toxicity of cadmium to the colonial hydroid *Laomedea loveni*. At 17.5°C cadmium concentrations inducing irreversible retraction of half of the polyps ranged from 12.4 µg/l at 25 g/kg salinity (Table 6). At 25 g/kg salinity the toxicity of cadmium decreased as temperature increased.

The effect of environmental factors on the acute toxicity of cadmium is also evident for the early life stages of saltwater vertebrates. Alderdice, et al. (1979a,b,c,) reported that salinity influenced the effects of cadmium on the volume, capsule strength, and osmotic response of embryos of the Pacific herring. Voyer, et al. (1979) reported a significant linear relationship between salinity and cadmium toxicity to Atlantic silverside embryos. Previous studies on the embryos of the winter flounder indicated a quadratic salinity-cadmium relationship (Voyer, et al. 1977).

Several studies have reported on the chronic sublethal effects of cadmium on saltwater fishes (Table 6). Significant reduction in gill tissue respiratory rates and the alteration of liver enzyme activity have been reported for the cunner after a 30-day exposure to 50 µg/l (MacInnes, et al. 1977). Dawson, et al. (1977) also reported a significant decrease in gill-tissue respiration for striped bass at 0.5 µg/l above ambient after a 30-day, but not a 90-day, exposure. A similar study on the winter flounder (Calabrese, et al. 1975) demonstrated a significant alteration in gill tissue respiration rates measured *in vitro* after a 60-day exposure to 5 µg/l. The significance of these sublethal effects on growth and reproduction have yet to be evaluated.

Summary

The results of acute toxicity tests on cadmium with 29 freshwater species range from 1 to 73,500 µg/l with both fish and invertebrates distributed throughout the range. The antagonistic effect of hardness on acute toxicity has been demonstrated with seven species. Chronic tests have been conducted on cadmium with 12 freshwater fish species and one invertebrate species. The seven available acute-chronic ratios are all between 66 and 431.

Freshwater aquatic plants are affected by cadmium at concentrations ranging from 2 to 7,400 µg/l. These values are in the same range as the acute toxicity values for fish and invertebrate species, and are considerably above the chronic values. Bioconcentration factors for cadmium reach 3,000 for some invertebrates and may be as high as 12,000 for some fish species.

The saltwater acute values for cadmium and five species of fishes ranged from 577 µg/l for larval Atlantic silversides to 114,000 µg/l for juvenile mummichog. Acute values for 26 species of invertebrates ranged from 15.5 µg/l for the mysid shrimp to 46,600 µg/l for the fiddler crab. The acute toxicity of cadmium seems to increase as salinity decreases and as temperature increases, although the magnitudes of the effects seem to vary with species. Two life cycle tests on Mysidopsis bahia under different test conditions resulted in similar chronic values of 5.5 and 8.0 µg/l, but the acute-chronic ratios were 2.8 and 14, respectively. These acute values appear to reflect the effects of salinity and temperature, whereas the chronic values apparently do not. Plant studies with microalgae report growth inhibition at 160 µg/l.

Tissue residues were reported for 1 species of algae, 10 species of invertebrates, and 1 species of fish. Bioconcentration factors for fish and crustaceans were generally less than 400, whereas those for bivalve molluscs were above 2,500 in long exposures, with no indication that steady-state was reached, and resulted in a Final Residue Value of 4.5 µg/l. Cadmium mortality is cumulative for exposure periods beyond four days. Chronic cadmium exposure resulted in significant effects on the growth of bay scallops at 78 µg/l and on reproduction of a copepod at 44 µg/l.

CRITERIA

For total recoverable cadmium the criterion (in µg/l) to protect freshwater aquatic life as derived using the Guidelines is the numerical value given by $e^{(1.05[\ln(\text{hardness})]-8.53)}$ as a 24-hour average, and the concentration (in µg/l) should not exceed the numerical value given by $e^{(1.05[\ln(\text{hardness})-3.73)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the criteria are 0.012, 0.025, and 0.051 µg/l, respectively, and the concentration of total recoverable cadmium should not exceed 1.5, 3.0 and 6.3 µg/l, respectively, at any time.

For total recoverable cadmium the criterion to protect saltwater aquatic life as derived using the Guidelines is 4.5 µg/l as a 24-hour average, and the concentration should not exceed 59 µg/l at any time.

Table 1. Acute values for cadmium

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
FRESHWATER SPECIES					
Rotifer, *Philodina acuticornis*	R, U	Cadmium chloride	25	500	Buikema, et al. 1974
Rotifer, *Philodina acuticornis*	R, U	Cadmium sulfate	25	200	Buikema, et al. 1974
Rotifer, *Philodina acuticornis*	R, U	Cadmium sulfate	81	300	Buikema, et al. 1974
Bristle worm, *Nais* sp.	S, U	-	50	1,700	Rehwoldt, et al. 1973
Snail (adult), *Amnicola* sp.	S, U	-	50	8,400	Rehwoldt, et al. 1973
Snail (adult), *Physa gyrina*	S, M	-	200	1,370	Wier & Walter, 1976
Snail (immature), *Physa gyrina*	S, M	-	200	410	Wier & Walter, 1976
Cladoceran, *Daphnia magna*	S, U	Cadmium chloride	45	65	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	S, M	Cadmium chloride	51	9.9	Chapman, Manuscript
Cladoceran, *Daphnia magna*	S, M	Cadmium chloride	104	33	Chapman, Manuscript
Cladoceran, *Daphnia magna*	S, M	Cadmium chloride	105	34	Chapman, Manuscript
Cladoceran, *Daphnia magna*	S, M	Cadmium chloride	197	63	Chapman, Manuscript
Cladoceran, *Daphnia magna*	S, M	Cadmium chloride	209	49	Chapman, Manuscript

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
Cladoceran, *Daphnia magna*	S, U	Cadmium nitrate	-	47	Canton & Adema, 1978
Cladoceran, *Daphnia pulex*	S, U	Cadmium nitrate	-	140	Canton & Adema, 1978
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	10.0	35.0	Giesy, et al. 1977
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	11.1	7.0	Giesy, et al. 1977
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	11.1	3.5	Giesy, et al. 1977
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	11.1	12.0	Giesy, et al. 1977
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	11.1	16.5	Giesy, et al. 1977
Cladoceran, *Simocephalus serrulatus*	S, M	Cadmium chloride	11.1	8.6	Giesy, et al. 1977
Scud, *Gammarus* sp.	S, U	-	50	70	Rehwoldt, et al. 1973
Mayfly, *Ephemerella grandis grandis*	FT, M	Cadmium chloride	-	28,000	Clubb, et al. 1975
Mayfly, *Ephemerella grandis grandis*	S, U	Cadmium sulfate	54	2,000	Warnick & Bell, 1969
Stonefly, *Pteronarcella badia*	FT, M	Cadmium chloride	-	18,000	Clubb, et al. 1975

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
Damselfly, Unidentified	S, U	-	50	8,100	Rehwoldt, et al. 1973
Midge, *Chironomus*	S, U	-	50	1,200	Rehwoldt, et al. 1973
Caddisfly, Unidentified	S, U	-	50	3,400	Rehwoldt, et al. 1973
American eel, *Anguilla rostrata*	S, M	-	55	820	Rehwoldt, et al. 1972
Chinook salmon (swim-up), *Oncorhynchus tshawytscha*	FT, M	Cadmium chloride	23	1.8	Chapman, 1978
Chinook salmon (parr), *Oncorhynchus tshawytscha*	FT, M	Cadmium chloride	23	3.5	Chapman, 1978
Rainbow trout, *Salmo gairdneri*	S, U	Cadmium chloride	-	6.0	Kumada, et al. 1980
Rainbow trout (swim-up), *Salmo gairdneri*	FT, M	Cadmium chloride	23	1.3	Chapman, 1978
Rainbow trout (parr), *Salmo gairdneri*	FT, M	Cadmium chloride	23	1.0	Chapman, 1978
Rainbow trout (2-mos), *Salmo gairdneri*	FT, M	Cadmium nitrate	-	6.6	Hale, 1977
Rainbow trout, *Salmo gairdneri*	FT, M	Cadmium sulfate	31	1.75	Davies, 1976
Rainbow trout, *Salmo gairdneri*	S, U	-	-	6	Kumada, et al. 1973
Rainbow trout, *Salmo gairdneri*	S, U	-	-	7	Kumada, et al. 1973
Brook trout, *Salvelinus fontinalis*	S, M	Cadmium sulfate	340 (calcium carbonate)	26	Carroll, et al. 1979

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
Brook trout, *Salvelinus fontinalis*	S, M	Cadmium sulfate	340 (calcium sulfate)	29	Carroll, et al. 1979
Brook trout, *Salvelinus fontinalis*	S, M	Cadmium sulfate	350 (magnesium carbonate)	3.8	Carroll, et al. 1979
Brook trout, *Salvelinus fontinalis*	S, M	Cadmium sulfate	330 (magnesium sulfate)	4.4	Carroll, et al. 1979
Brook trout, *Salvelinus fontinalis*	S, M	Cadmium sulfate	44 (sodium sulfate)	2.4	Carroll, et al. 1979
Goldfish, *Carassius auratus*	S, U	Cadmium chloride	20	2,340	Pickering & Henderson, 1966
Goldfish, *Carassius auratus*	S, M	Cadmium chloride	20	2,130	McCarty, et al. 1978
Goldfish, *Carassius auratus*	S, M	Cadmium chloride	140	46,800	McCarty, et al. 1978
Fathead minnow, *Pimephales promelas*	S, U	Cadmium chloride	20	1,050	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	Cadmium chloride	20	630	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	Cadmium chloride	360	72,600	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	Cadmium chloride	360	73,500	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	FT, M	Cadmium sulfate	201	11,000	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT, M	Cadmium sulfate	201	12,000	Pickering & Gast, 1972

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	FT, M	Cadmium sulfate	201	6,400	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT, M	Cadmium sulfate	201	2,000	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT, M	Cadmium sulfate	201	4,500	Pickering & Gast, 1972
Northern squawfish, *Ptychocheilus oregonensis*	F, M	Cadmium chloride	20-30	1,092	Andros & Garton, 1980
Northern squawfish, *Ptychocheilus oregonensis*	F, M	Cadmium chloride	20-30	1,104	Andros & Garton, 1980
Carp, *Cyprinus carpio*	S, M	-	55	240	Rehwoldt, et al. 1972
Banded killifish, *Fundulus diaphanus*	S, M	-	55	110	Rehwoldt, et al, 1972
Flagfish, *Jordanella floridae*	FT, M	Cadmium chloride	44	2,500	Spehar, 1976a
Mosquitofish, *Gambusia affinis*	FT, M	Cadmium chloride	10.0	1,500	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT, M	Cadmium chloride	10.0	1,500	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT, M	Cadmium chloride	10.0	2,600	Gisey, et al. 1977
Mosquitofish, *Gambusia affinis*	FT, M	Cadmium chloride	11.1	900	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT, M	Cadmium chloride	11.1	2,200	Giesy, et al. 1977
Guppy, *Lebistes reticulatus*	S, U	Cadmium chloride	20	1,270	Pickering & Henderson, 1966

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Reference
Threespine stickleback, *Gasterosteus aculeatus*	S, U	Cadmium chloride	115	6,500	Pascoe & Cram, 1977
Threespine stickleback, *Gasterosteus aculeatus*	R, M	Cadmium chloride	103-111	23,000	Pascoe & Mattey, 1977
White perch, *Morone americanus*	S, M	-	55	8,400	Rehwoldt, et al. 1972
Striped bass, *Morone saxatilus*	S, M	-	55	1,100	Rehwoldt, et al. 1972
Striped bass (larvae), *Morone saxatilus*	S, U	Cadmium chloride	70	1	Hughes, 1973
Striped bass (fingerling), *Morone saxatilus*	S, U	Cadmium chloride	70	2	Hughes, 1973
Green sunfish, *Lepomis cyanellus*	S, U	Cadmium chloride	20	2,840	Pickering & Henderson, 1966
Green sunfish, *Lepomis cyanellus*	S, U	Cadmium chloride	360	66,000	Pickering & Henderson, 1966
Green sunfish, *Lepomis cyanellus*	FT, M	Cadmium chloride	335	20,500	Jude, 1973
Pumpkinseed, *Lepomis gibbosus*	S, M	-	55	1,500	Rehwoldt, et al. 1972
Bluegill, *Lepomis macrochirus*	S, U	Cadmium chloride	20	1,940	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	FT, M	Cadmium chloride	207	21,100	Eaton, 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
		SALTWATER SPECIES			
Polychaete worm (adult), Capitella capitata	S, U	Cadmium chloride	7,500	-	Reish, et al. 1976
Polychaete worm (larva), Capitella capitata	S, U	Cadmium chloride	200	1,220	Reish, et al. 1976
Polychaete worm (adult), Neanthes arenaceodentata	S, U	Cadmium chloride	12,000	-	Reish, et al. 1976
Polychaete worm (juvenile), Neanthes arenaceodentata	S, U	Cadmium chloride	12,500	12,200	Reish, et al. 1976
Polychaete worm, Nereis virens	S, U	Cadmium chloride	9,300	-	Eisler & Hennekey, 1977
Polychaete worm, Nereis virens	S, U	Cadmium chloride	11,000	10,100	Eisler, 1971
Bay scallop (juvenile), Argopecten irradians	S, U	Cadmium chloride	1,480	1,480	Nelson, et al. 1976
American oyster (larva), Crassostrea virginica	S, U	Cadmium chloride	3,800	3,800	Calabrese, et al. 1973
Soft shelled clam, Mya arenaria	S, U	Cadmium chloride	2,500	-	Eisler & Hennekey, 1977
Soft shelled clam, Mya arenaria	S, U	Cadmium chloride	2,200	-	Eisler, 1971
Soft shelled clam, Mya arenaria	S, U	Cadmium chloride	850	1,670	Eisler, 1977
Mussel, Mytilus edulis	S, U	Cadmium chloride	25,000	-	Eisler, 1971
Mussel, Mytilus edulis	S, M	Cadmium chloride	1,620	-	Ahsanullah, 1976

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Mussel, *Mytilus edulis*	FT, M	Cadmium chloride	3,600	-	Ahsanullah, 1976
Mussel, *Mytilus edulis*	FT, M	Cadmium chloride	4,300	3,940	Ahsanullah, 1976
Mud snail, *Nassarius obsoletus*	S, U	Cadmium chloride	35,000	-	Eisler & Hennekey, 1977
Mud snail, *Nassarius obsoletus*	S, U	Cadmium chloride	10,500	19,200	Eisler, 1971
Oyster drill, *Urosalpinx cinerea*	S, U	Cadmium chloride	6,600	6,600	Eisler, 1971
Copepod, *Acartia clausi*	S, U	Cadmium chloride	144	144	U.S. EPA, 1980
Copepod, *Acartia tonsa*	S, U	Cadmium chloride	90	-	Sosnowski & Gentile, 1978
Copepod, *Acartia tonsa*	S, U	Cadmium chloride	122	-	Sosnowski & Gentile, 1978
Copepod, *Acartia tonsa*	S, U	Cadmium chloride	220	-	Sosnowski & Gentile, 1978
Copepod, *Acartia tonsa*	S, U	Cadmium chloride	337	169	Sosnowski & Gentile, 1978
Copepod, *Eurytemora affinis*	S, U	Cadmium chloride	1,080	1,080	U.S. EPA, 1980
Copepod, *Nitocra spinipes*	S, U	Cadmium chloride	1,800	1,800	Bengtsson, 1978
Copepod, *Pseudodiaptomus coronatus*	S, U	Cadmium chloride	1,708	1,710	U.S. EPA, 1980
Copepod, *Tigriopus japonicus*	S, U	Cadmium chloride	5,290	5,290	U.S. EPA, 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Mysid shrimp, *Mysidopsis bahia*	FT, M	Cadmium chloride	15.5	-	Nimmo, et al. 1977a
Mysid shrimp, *Mysidopsis bahia*	FT, M	Cadmium chloride	110	41.3	U.S. EPA, 1980
Mysid shrimp, *Mysidopsis bigelowi*	F, M	Cadmium chloride	135	135	U.S. EPA, 1980
Blue crab (juveniles), *Callinectes sapidus*	S, U	Cadmium chloride	11,600	-	Frank & Robertson, 1979
Blue crab (juveniles), *Callinectes sapidus*	S, U	Cadmium chloride	4,700	-	Frank & Robertson, 1979
Blue crab (juveniles), *Callinectes sapidus*	S, U	Cadmium chloride	320	2,590	Frank & Robertson, 1979
Green crab, *Carcinus maenas*	S, U	Cadmium chloride	4,100	4,100	Eisler, 1971
Sand shrimp, *Crangon septemspinosa*	S, U	Cadmium chloride	320	320	Eisler, 1971
American lobster (larva), *Homarus americanus*	S, U	Cadmium chloride	78	78	Johnson & Gentile, 1979
Hermit crab, *Pagurus longicarpus*	S, U	Cadmium chloride	320	-	Eisler, 1971
Hermit crab, *Pagurus longicarpus*	S, U	Cadmium chloride	1,300	645	Eisler & Hennekey, 1977
Grass shrimp, *Palaemonetes vulgaris*	S, U	Cadmium chloride	420	-	Eisler, 1971
Grass shrimp, *Palaemonetes vulgaris*	FT, M	Cadmium chloride	760	760	Nimmo, et al. 1977b
Pink shrimp, *Penaeus duorarum*	FT, M	Cadmium chloride	3,500	3,500	Nimmo, et al. 1977b

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	46,600	-	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	37,000	-	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	32,300	-	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	23,300	-	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	10,400	-	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S, U	Cadmium chloride	6,800	21,200	O'Hara, 1973
Starfish, *Asterias forbesi*	S, U	Cadmium chloride	7,100	-	Eisler & Hennekey, 1977
Starfish, *Asterias forbesi*	S, U	Cadmium chloride	820	2,410	Eisler, 1971
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Cadmium chloride	50,000	50,000	Eisler, 1971
Striped killifish (adult), *Fundulus majalis*	S, U	Cadmium chloride	21,000	21,000	Eisler, 1971
Mummichog (adult), *Fundulus heteroclitus*	S, U	Cadmium chloride	49,000	-	Eisler, 1971
Mummichog (adult), *Fundulus heteroclitus*	S, U	Cadmium chloride	22,000	-	Eisler & Hennekey, 1977
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	114,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	92,000	-	Voyer, 1975

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	78,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	73,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	63,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	31,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	30,000	-	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S, U	Cadmium chloride	29,000	50,600	Voyer, 1975
Atlantic silverside (adult), *Menidia menidia*	S, U	Cadmium chloride	2,032	-	U.S. EPA, 1980
Atlantic silverside (juvenile), *Menidia menidia*	S, U	Cadmium chloride	28,532	-	U.S. EPA, 1980
Atlantic silverside (juvenile), *Menidia menidia*	S, U	Cadmium chloride	13,652	-	U.S. EPA, 1980
Atlantic silverside (larva), *Menidia menidia*	S, U	Cadmium chloride	1,054	-	U.S. EPA, 1980
Atlantic silverside (larva), *Menidia menidia*	S, U	Cadmium chloride	577	3,400	U.S. EPA, 1980
Winter flounder (larva), *Pseudopleuronectes americanus*	S, U	Cadmium chloride	14,297	-	U.S. EPA, 1980
Winter flounder (larva), *Pseudopleuronectes americanus*	S, U	Cadmium chloride	602	2,930	U.S. EPA, 1980

Table 1. (Continued)

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* S= static, FT = flow-through, R = renewal, M = measured, U = unmeasured

**Values are expressed as cadmium, not as the compound.

Freshwater

Acute Toxicity vs. Hardness

Species	Slope	Intercept	r	N
Rotifer, Philodina acuticornis	-0.045	5.90	-0.07	3
Cladoceran, Daphnia magna	0.48	1.39	0.44	6
Rainbow trout, Salmo gairdneri	1.44	-4.37	0.88	3
Brook trout, Salvelinus fontinalis	0.72	-1.86	0.57	5
Goldfish, Carassius auratus	1.56	3.03	1.0	3
Fathead minnow, Pimephales promelas	1.25	2.66	0.83	9
Green sunfish, Lepomis cyanellus	0.90	5.23	0.94	3
Bluegill, Lepomis macrochirus	1.02	4.51	1.0	2

Arithmetic mean acute slope = 1.05 (N=7; see text)

Table 2. Chronic values for cadmium

Species	Test*	Chemical	Hardness (mg/l as $CaCO_3$)	Limits** (µg/l)	Chronic Value** (µg/l)	Reference
			FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Cadmium chloride	45	0.17-0.7	0.34	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	LC	Cadmium chloride	53	0.08-0.29	0.15	Chapman, Manuscript
Cladoceran, *Daphnia magna*	LC	Cadmium chloride	103	0.16-0.28	0.21	Chapman, Manuscript
Cladoceran, *Daphnia magna*	LC	Cadmium chloride	209	0.21-0.91	0.44	Chapman, Manuscript
Coho salmon (Lake Superior), *Oncorhynchus kisutch*	ELS	Cadmium chloride	44	1.3-3.4	2.1	Eaton, et al. 1978
Coho salmon (West Coast), *Oncorhynchus kisutch*	ELS	Cadmium chloride	44	4.1-12.5	7.2	Eaton, et al. 1978
Brook trout, *Salvelinus fontinalis*	ELS	Cadmium chloride	44	1.1-3.8	2.0	Eaton, et al. 1978
Brook trout, *Salvelinus fontinalis*	LC	Cadmium chloride	44	1.7-3.4	2.4	Benoit, et al. 1976
Brook trout, *Salvelinus fontinalis*	ELS	Cadmium chloride	36	1-3	1.7	Sauter, et al. 1976
Brook trout, *Salvelinus fontinalis*	ELS	Cadmium chloride	187	7-12	9.2	Sauter, et al. 1976
Lake trout, *Salvelinus namaycush*	ELS	Cadmium chloride	44	4.4-12.3	7.4	Eaton, et al. 1978
Brown trout, *Salmo trutta*	ELS	Cadmium chloride	44	3.8-11.7	6.7	Eaton, et al. 1978
Northern pike, *Esox lucius*	ELS	Cadmium chloride	44	4.2-12.9	7.4	Eaton, et al. 1978

Table 2. (Continued)

Species	Test*	Chemical	Hardness (mg/l as $CaCO_3$)	Limits** (µg/l)	Chronic Value** (µg/l)	Reference
Fathead minnow, Pimephales promelas	LC	Cadmium sulfate	201	37-57	46	Pickering & Gast, 1972
White sucker, Catostomus commersoni	ELS	Cadmium chloride	44	4.2-12.0	7.1	Eaton, et al. 1978
Channel catfish, Ictalurus punctatus	ELS	Cadmium chloride	37	11-17	13.7	Sauter, et al. 1976
Channel catfish, Ictalurus punctatus	ELS	Cadmium chloride	185	12-17	14.3	Sauter, et al. 1976
Flagfish, Jordanella floridae	LC	Cadmium chloride	44	4.1-8.1	5.8	Spehar, 1976a
Smallmouth bass, Micropterus dolomieui	ELS	Cadmium chloride	44	4.3-12.7	7.4	Eaton, et al. 1978
Bluegill, Lepomis macrochirus	LC	Cadmium sulfate	207	31-80	50	Eaton, 1974
Walleye, Stizostedion vitreum	ELS	Cadmium chloride	35	9-25	15	Sauter, et al. 1976
		SALTWATER SPECIES				
Mysid shrimp, Mysidopsis bahia	LC	Cadmium chloride	-	4.8-6.4	5.5	Nimmo et al. 1977a
Mysid shrimp, Mysidopsis bahia	LC	Cadmium chloride	-	5.5-11.5	8.0	U.S. EPA, 1980

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* ELS = early life stage, LC = life cycle or partial life cycle

**Values are expressed as cadmium, not as the compound.

Table 2. (Continued)

Acute-Chronic Ratios

Species	Hardness (mg/l as $CaCO_3$)	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	45	65	0.34	191
Cladoceran, *Daphnia magna*	53	9.9	0.15	66
Cladoceran, *Daphnia magna*	103	33	0.21	157
Cladoceran, *Daphnia magna*	209	49	0.44	111
Fathead minnow, *Pimephales promelas*	201	5, 970	46	130
Flagfish, *Jordanella floridae*	44	2,500	5.8	431
Bluegill, *Lepomis macrochirus*	207	21,100	50	422
Mysid shrimp, *Mysidopsis bahia*	-	15.5	5.5	2.8
Mysid shrimp, *Mysidopsis bahia*	-	110	8.0	14

Table 2. (Continued)

Freshwater Species Mean Chronic Intercepts

Rank*	Species	Species Mean Chronic Intercept µg/l)
13	Walleye, *Stizostedion vitreum*	0.359
12	Bluegill, *Lepomis macrochirus*	0.185
11	Fathead minnow, *Pimephales promelas*	0.176
10	Lake trout, *Salvelinus namaycush*	0.139
9	Northern pike, *Esox lucius*	0.139
8	Smallmouth bass, *Micropterus dolomieui*	0.139
7	Channel catfish, *Ictalurus punctatus*	0.136
6	White sucker, *Catostomus commersoni*	0.134
5	Brook trout, *Salvelinus fontinalis*	0.126
4	Flagfish, *Jordanella floridae*	0.109
3	Coho salmon, *Oncorhynchus kisutch*	0.0731
2	Brown trout, *Salmo trutta*	0.0399
1	Cladoceran, *Daphnia magna*	0.00248

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* Ranked from least sensitive to most sensitive based on Species Mean Chronic Intercept.

Table 3. Species mean acute intercepts and values and acute-chronic ratios for cadmium

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
		FRESHWATER SPECIES	
29	Snail, *Amnicola* sp.	138	-
28	Mosquitofish, *Gambusia affinis*	135	-
27	Goldfish, *Carassius auratus*	134	-
26	Damselfly, Unidentified	133	-
25	White perch, *Morone americanus*	125	-
24	Green sunfish, *Lepomis cyanellus*	91.4	-
23	Threespine stickleback, *Gasterosteus aculeatus*	86.7	-
22	Bluegill, *Lepomis macrochirus*	80.7	422
21	Caddisfly, Unidentified	55.9	-
20	Guppy, *Lebistes reticulatus*	54.7	-
19	Flagfish, *Jordanella floridae*	47.0	431
18	Fathead minnow, *Pimephales promelas*	38.2	130
17	Northern squawfish, *Ptychocheilus oregonensis*	35.9	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
16	Mayfly, *Ephemerella grandis grandis*	30.3	-
15	Bristle worm, *Nais*, sp.	28.0	-
14	Pumpkinseed, *Lepomis gibbosus*	22.3	-
13	Midge, *Chironomus*	19.7	-
12	American eel, *Anguilla rostrata*	12.2	-
11	Rotifer, *Philodina acuticornis*	7.01	-
10	Carp, *Cyprinus carpio*	3.57	-
9	Snail, *Physa gyrina*	2.87	-
8	Banded killifish, *Fundulus diaphanus*	1.67	-
7	Scud, *Gammarus* sp.	1.15	-
6	Cladoceran, *Simocephalus serrulatus*	0.87	-
5	Cladoceran, *Daphnia magna*	0.29	122
4	Chinook salmon, *Oncorhynchus tshawytscha*	0.09	-
3	Rainbow trout, *Salmo gairdneri*	0.04	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
2	Brook trout, *Salvelinus fontinalis*	0.03	-
1	Striped bass, *Morone saxitalis*	0.02	-

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	SALTWATER SPECIES		
31	Mummichog, *Fundulus heteroclitus*	50,600	-
30	Sheepshead minnow, *Cyprinodon variegatus*	50,000	-
29	Fiddler crab, *Uca pugilator*	21,200	-
28	Striped killifish, *Fundulus majalis*	21,000	-
27	Mud snail, *Nassarius obsoletus*	19,200	-
26	Polychaete worm, *Neanthes arenaceodentata*	12,200	-
25	Polychaete worm, *Nereis virens*	10,100	-
24	Oyster drill, *Urosalpinx cinerea*	6,600	-
23	Copepod, *Tigriopus japonicus*	5,290	-
22	Green crab, *Carcinus maenus*	4,100	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
21	Mussel, *Mytilus edulis*	3,940	-
20	American oyster, *Crassostrea virginica*	3,800	-
19	Pink shrimp, *Penaeus duorarum*	3,500	-
18	Atlantic silverside *Menidia menidia*	3,440	-
17	Winter flounder, *Pseudopleuronectes americanus*	2,930	-
16	Blue crab, *Callinectes sapidus*	2,590	-
15	Starfish, *Asterias forbesi*	2,410	-
14	Copepod, *Nitocra spinipes*	1,800	-
13	Copepod, *Pseudodiaptomus cornatus*	1,710	-
12	Soft shelled clam, *Mya arenaria*	1,670	-
11	Bay scallop, *Argopecten irradians*	1,480	-
10	Polychaete worm, *Capitella capitata*	1,220	-
9	Copepod, *Eurytemora affinis*	1,080	-
8	Grass shrimp, *Palaemonetes vulgaris*	760	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
7	Hermit crab *Pagurus longicarpus*	645	-
6	Sand shrimp, *Crangon septemspinosa*	320	-
5	Copepod, *Acartia tonsa*	169	-
4	Copepod, *Acartia clausi*	144	-
3	Mysid shrimp, *Mysidopsis bigelowi*	135	-
2	American lobster, *Homarus americanus*	78	-
1	Mysid shrimp, *Mysidopsis bahia*	41.3	6.3

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* Ranked from least sensitive to most sensitive based on species mean acute intercept or value.

Freshwater

Final Acute Intercept = 0.024 µg/l

Natural logarithm of 0.024 = -3.73

Acute slope = 1.05 (see Table 1)

Final Acute Equation = $e^{(1.05[\ln(\text{hardness})]-3.73)}$

Final Acute-Chronic Ratio = 122 (see text)

Table 3. (Continued)

Final Chronic Intercept = (0.024 μg/l)/122 = 0.000197 μg/l

Natural logarithm of 0.000197 = -8.53

Chronic slope = 1.05 (see text)

Final Chronic Equation = $e^{(1.05[\ln(\text{hardness})]-8.53)}$

Saltwater

Final Acute Value = 58.6 μg/l

Table 4. Plant values for cadmium

Species	Chemical	Hardness (mg/l as CaCO3)	Effect	Result* (µg/l)	Reference
		FRESHWATER SPECIES			
Diatom, *Asterionella formosa*	-	-	Factor of 10 growth rate decrease	2	Conway, 1978
Diatom, *Scenedesmus quadracauda*	Cadmium chloride	-	Reduction in cell count	6.1	Klass, et al. 1974
Green alga, *Chlorella pyrenoidosa*	-	-	Reduction in growth	250	Hart & Scaife, 1977
Green alga, *Chlorella vulgaris*	-	-	Reduction in growth	50	Hutchinson & Stokes, 1975
Green alga, *Chlorella vulgaris*	Cadmium chloride	-	50% reduction in growth	60	Rosko & Rachlin, 1977
Green alga, *Selanastrum capricornutum*	Cadmium chloride	-	Reduction in growth	50	Bartlett, et al. 1974
Algae (mixed spp.)	Cadmium chloride	11.1	Significant reduction in population	5	Giesy, et al. 1979
Fern, *Salvina natans*	Cadmium nitrate	-	Reduction in number of fronds	10	Hutchinson & Czyrska, 1972
Eurasian watermilfoil, *Myriophyllum spicatum*	-	-	50% root weight inhibition	7,400	Stanley, 1974
Duckweed, *Lemna valdiviana*	Cadmium nitrate	-	Reduction in number of fronds	10	Hutchinson & Cyrska, 1972
		SALTWATER SPECIES			
Alga, *Thalassiosira pseudonana*	Cadmium chloride	-	96-hr EC50 growth rate	160	U.S. EPA, 1980

Table 4. (Continued)

Species	Chemical	Hardness (mg/l as CaCO3)	Effect	Result* (µg/l)	Reference
Alga, *Skeletonema costatum*	Cadmium chloride	-	96 hr EC50 growth rate	175	U.S. EPA, 1980

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* Results are expressed as cadmium, not as the compound.

Table 5. Residues for cadmium

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
FRESHWATER SPECIES					
Aufwuchs (attached microscopic plants and animals	-	Cadmium chloride	7,100 at 5 µg/l	52 wks	Giesy, et al. 1979
Aufwuchs (attached microscopic plants and animals	-	Cadmium chloride	5,800 at 10 µg/l	52 wks	Giesy, et al. 1979
Duckweed, *Lemna valdiviana*	Whole plant	Cadmium nitrate	603	21	Hutchinson & Czyrska, 1972
Fern, *Salvinia natans*	Whole plant	Cadmium nitrate	960	21	Hutchinson & Czyrska, 1972
Rush, *Juncus diffusissimus*	Leaves	Cadmium chloride	1,300	52 wks	Giesy, et al. 1979
Pond weed, *Callitriche heterophylla*	Whole plant	Cadmium chloride	1,200	52 wks	Giesy, et al. 1979
Cladoceran, *Daphnia magna*	Whole body	Cadmium sulfate	320	2-4	Poldoski, 1979
Crayfish, *Orconectes propinquus*	Whole body	-	184	8	Gillespie, et al. 1977
Stonefly, *Pteronarcys dorsata*	Whole body	Cadmium chloride	373	28	Spehar, et al. 1978
Mayfly, *Ephemerella* sp.	Whole body	Cadmium chloride	1,630 at 5 µg/l	52 wks	Giesy, et al. 1979
Mayfly, *Ephemerella* sp.	Whole body	Cadmium chloride	3,520 at 10 µg/l	52 wks	Giesy, et al. 1979
Dragonfly, *Pantala hymenea*	Whole body	Cadmium chloride	736 at 5 µg/l	52 wks	Giesy, et al. 1979
Dragonfly, *Pantala hymenea*	Whole body	Cadmium chloride	680 at 10 µg/l	52 wks	Giesy, et al. 1979

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
Dragonfly,, *Ischnura* sp.	Whole body	Cadmium chloride	1,300 at 5 µg/l	52 wks	Giesy, et al. 1979
Dragonfly, *Ischnura* sp.	Whole body	Cadmium chloride	928 at 10 µg/l	52 wks	Giesy, et al. 1979
Caddisfly, *Hydropsyche betteni*	Whole body	Cadmium chloride	4,190	28	Spehar, et al. 1978
Beetle, Dytiscidae	Whole body	Cadmium chloride	164 at 5 µg/l	52 wks	Giesy, et al. 1979
Beetle, Dytiscidae	Whole body	Cadmium chloride	260 at 10 µg/l	52 wks	Giesy, et al. 1979
Midge, Chironomidae	Whole body	Cadmium chloride	2,220 at 5 µg/l	52 wks	Giesy, et al. 1979
Midge, Chironomidae	Whole body	Cadmium chloride	1,830 at 10 µg/l	52 wks	Giesy, et al. 1979
Biting midge, Ceratopoganidae	Whole body	Cadmium chlorde	936 at 5 µg/l	52 wks	Giesy, et al. 1979
Biting midge, Ceratopoganidae	Whole body	Cadmium chloride	662 at 10 µg/l	52 wks	Giesy, et al. 1979
Snail, *Physa integra*	Whole body	Cadmium chloride	1,750	28	Spehar, et al. 1978
Rainbow trout, *Salmo gairdneri*	Whole body	-	540	140	Kumada, et al. 1973
Rainbow trout, *Salmo gairdneri*	Whole body	Cadmium chloride	33 at 4 µg/l	10 wks	Kumada et al. 1980
Brook trout, *Salvelinus fontinalis*	Muscle	Cadmium chloride	3	490	Benoit, et al. 1976
Brook trout, *Salvelinus fontinalis*	Muscle	Cadmium chloride	151	84	Benoit, et al. 1976
Brook trout, *Salvelinus fontinalis*	Muscle	Cadmium chloride	10	93	Sangalang & Freeman, 1979

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
Flagfish, *Jordanella floridae*	Whole body	Cadmium chloride	1,988	30	Spehar, 1976b
Mosquitofish, *Gambusia affinis*	Whole body	Cadmium chloride	4,100 at 0.02 µg/l (0.115 ppm in food)	8 wks	Williams & Giesy, 1978
Mosquitofish, *Gambusia affinis*	Whole body	Cadmium chloride	938 at 10 µg/l (0.115 ppm in food)	8 wks	Williams & Giesy, 1978
Mosquitofish, *Gambusia affinis*	Whole body (not steady state)	Cadmium chloride	7,440 at 5 µg/l	180	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	Whole body (not steady state)	Cadmium chloride	12,400 at 10 µg/l	180	Giesy, et al. 1977
Threespined stickleback, *Gasterosteus aculeatus* L.	Whole body	Cadmium chloride	900	33	Pascoe & Mattey, 1977
		SALTWATER SPECIES			
Alga, *Prasinocladus tricornutum*	-	Cadmium iodide	670	5	Kerfoot & Jacobs, 1976
Hydroid polyp, *Laomedea loveni*	Whole organism	Cadmium chloride	153	10	Theede, et al. 1979
Polychaete worm, *Ophryotrocha diadema*	Whole body	Cadmium chloride	3,160	64	Klockner, 1979
American oyster, *Crassostrea virginica*	Soft parts	Cadmium chloride	2,600	280	Zaroogian & Cheer, 1976
American oyster, *Crassostrea virginica*	Soft parts	Cadmium chloride	3,650	280	Zaroogian, 1979

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
American oyster, Crassostrea virginica	Soft parts	Cadmium nitrate	1,220	98	Schuster & Pringle, 1969
Soft shell clam, Mya arenaria	Soft parts	Cadmium nitrate	160	70	Pringle, et al. 1968
Quahaug, Mercenaria mercenaria	Soft parts	Cadmium nitrate	83	40	Kerfoot & Jacobs, 1976
Bay scallop, Aquipecten irradians	Muscle	Cadmium chloride	2,040	42	Pesch & Stewart, 1980
Common mussel, Mytilus edulis	Soft parts	Cadmium chloride	113	28	George & Coombs, 1977
Common mussel, Mytilus edulis	Soft parts	Cadmium chloride	306	35	Phillips, 1976
Pink shrimp, Penaeus duorarm	Whole body	Cadmium chloride	57	30	Nimmo, et al. 1977b
Grass shrimp, Paleomonetes pugio	Whole body	Cadmium chloride	22	42	Pesch & Stewart, 1980
Grass shrimp, Palaemonetes vulgaris	Whole body	Cadmium chloride	307	28	Nimmo, et al. 1977b
Grass shrimp, Palaemonetes pugio	Whole body	Cadmium chloride	203	28	Nimmo, et al. 1977b

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
Crab, *Carcinus maenas*	Muscle	Cadmium chloride	5	68	Wright, 1977
Crab, *Carcinus maenas*	Muscle	Cadmium chloride	7	40	Jennings & Rainbow, 1979

Maximum Permissible Tissue Concentration

Species	Effect	Concentration (mg/kg)	Reference
Mallard, *Anas platyrhynchus*	Kidney tubule degeneration; significant testis weight reduction; evidence of inhibited spermatozoa production	200 mg/kg in food for 90 days	White & Finley, 1978 (a&b)
Man	Emitic threshold	13-5 mg/kg	Anon., 1950

Freshwater:

Geometric mean of all whole body BCF values = 766

Final Residue Value = (200 mg/kg)/766 = 0.26 mg/kg = 260 µg/l

Saltwater:

Geometric mean BCF for long-term exposure of oyster = 3,080

Final Residue Value = (14 mg/kg)/3,080 = 0.0045 mg/kg = 4.5 µg/l

Table 6. Other data for cadmium

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
		FRESHWATER SPECIES				
Mixed natural fungi and bacterial colonies on leaf litter	Cadmium chloride	10.7	28 wks	Inhibition of leaf decompositon	5	Giesy, 1978
Mixed macroinvertebrates	Cadmium chloride	11.1	52 wks	Reduction in mean total numbers and in numbers of taxa	5	Giesy, et al. 1979
Cladoceran, Daphnia pulex	Cadmium chloride	57	140 days	Reduced reproduction	1	Bertram & Hart, 1979
Cladoceran, Daphnia pulex	Cadmium chloride	57	96 hrs	LC50	47	Bertram & Hart, 1979
Cladoceran, Daphnia pulex	Cadmium chloride	57	72 hrs	LC50	62	Bertram & Hart, 1979
Cladoceran, Daphnia galeata mendotae	Cadmium chloride	-	22 wks	50% reduction in relative mean numbers	7.7	Marshall, 1978
Cladoceran, Daphnia galeata mendotae	Cadmium chloride	-	22 wks	Reduced biomass	4.0	Marshall, 1978
Annelid, Pristina sp.	Cadmium chloride	11.1	52 wks	Population reduction	5	Giesy, et al. 1979
Copepod, Eucyclops agilis	Cadmium chloride	11.1	52 wks	Popultion reduction	5	Giesy, et al. 1979
Crayfish, Cambarus latimanus	Cadmium chloride	11.1	5 mo	Significant mortality as compared to controls	5	Thorp, et al. 1979
Mayfly, Ephemerella sp.	Cadmium chloride	44-48	28 days	LC50	<3.0	Spehar, et al. 1978

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Midge, Tanytarsus dissimilis	Cadmium chloride	47	10 days	LC50	3.8	Anderson, et al. 1980
Snail (embryo), Amnicola sp.	-	50	96 hrs	LC50	3,800	Rehwoldt, et al. 1973
Snail, Physa integra	Cadmium chloride	44-48	28 days	LC50	10.4	Spehar, et al. 1978
Coho salmon (juvenile), Oncorhynchus kisutch	Cadmium chloride	22	217 hrs	LC50	2.0	Chapman & Stevens, 1978
Coho salmon (adult), Oncorhynchus kisutch	Cadmium chloride	22	215 hrs	LC50	3.7	Chapman & Stevens, 1978
Chinook salmon (alevin), Oncorhynchus tshawytscha	Cadmium chloride	23	200 hrs	LC10	18-26	Chapman, 1978
Chinook salmon (swim-up), Oncorhynchus tshawytscha	Cadmium chloride	23	200 hrs	LC10	1.2	Chapman, 1978
Chinook salmon (parr), Oncorhynchus tshawytscha	Cadmium chloride	23	200 hrs	LC10	1.3	Chapman, 1978
Chinook salmon (smolt), Oncorhynchus tshawytscha	Cadmium chloride	23	200 hrs	LC10	1.5	Chapman, 1978
Brook trout, Salvelinus fontinalis	Cadmium chloride	10	21 days	Testicular damage (blood vessel collapse, reduced 11-ketotestosterone synthesis)	20	Sangalang & O'Halloran, 1972, 1973
Rainbow trout, Salmo gairdneri	Cadmium stearate	-	96 hrs	LC50	6.0	Kumada, et al. 1980
Rainbow trout, Salmo gairdneri	Cadmium acetate	-	96 hrs	LC50	6.2	Kumada, et al. 1980

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	Cadmium chloride	104	28 days	LC50	130	Birge, 1978
Rainbow trout, *Salmo gairdneri*	-	-	240 hrs	LC50	7	Kumada, et al. 1973
Rainbow trout, *Salmo gairdneri*	-	-	240 hrs	LC50	5	Kumada, et al. 1973
Rainbow trout (adult), *Salmo gairdneri*	Cadmium chloride	54	408 hrs	LC50	5.2	Chapman & Stevens, 1978
Rainbow trout (alevin), *Salmo gairdneri*	Cadmium chloride	23	186 hrs	LC10	>6	Chapman, 1978
Rainbow trout (swim-up), *Salmo gairdneri*	Cadmium chloride	23	200 hrs	LC10	1.0	Chapman, 1978
Rainbow trout (parr), *Salmo gairdneri*	Cadmium chloride	23	200 hrs	LC10	0.7	Chapman, 1978
Rainbow trout (smolt), *Salmo gairdneri*	Cadmium chloride	23	200 hrs	LC10	0.8	Chapman, 1978
Rainbow trout, *Salmo gairdneri*	Cadmium sulfate	326	96 hrs	LC20	20	Davies, 1976
Rainbow trout, *Salmo gairdneri*	Cadmium stearate	-	10 wks	BCF	27	Kumada, et al. 1980
Rainbow trout, *Salmo gairdneri*	Cadmium stearate	-	10 wks	BCF	40	Kumada, et al. 1980
Rainbow trout, *Salmo gairdneri*	Cadmium acetate	-	10 wks	BCF	63	Kumada, et al. 1980
Rainbow trout, *Salmo gairdneri*	Cadmium chloride	125	10 days	LC50 (18°C)	10-30	Roch & Maly, 1979
Rainbow trout, *Salmo gairdneri*	Cadmium chloride	125	10 days	LC50 (12°C)	30	Roch & Maly, 1979

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	Cadmium chloride	125	10 days	LC50 (6°C)	30-100	Roch & Maly, 1979
Goldfish, *Carassius auratus*	Cadmium chloride	195	7 days	LC50	170	Birge, 1978
Goldfish, *Carasius auratus*	-	-	50 days	Reduced plasma sodium level (osmoregulatory changes)	44.5	McCarty & Houston, 1976
Mosquitofish, *Gambusia affinis*	Cadmium chloride	-	8 wks	BCF	6,100 at 0.02 µg/l & 1.13 ppm cadmium spiked into food	Williams & Giesy, 1978
Mosquitofish, *Gambusia affinis*	Cadmium chloride	11	8 wks	BCF	1,430 at 10 µg/l & 1.13 ppm cadmium spiked into food	Williams & Giesy, 1978
Threespine stickleback, *Gasterosteus aculeatus*	Cadmium chloride	-	33 days	LC50	0.8	Pascoe & Mattey, 1977
Largemouth bass, *Micropterus salmoides*	Cadmium chloride	99	8 days	LC50	1,640	Birge, et al. 1978
Salamander, *Ambystoma opacum*	Cadmium chloride	99	8 days	LC50	150	Birge, et al. 1978
Toad, *Gastrophyryne carolinensis*	Cadmium chloride	195	7 days	LC50	40	Birge, 1978
			SALTWATER SPECIES			
Colonial hydroid, *Campanularia flexuosa*	-	-	-	Enzyme inhibition	40-75	Moore & Stebbing, 1976

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Colonial hydroid, *Campanularia flexuosa*	-	-	11 days	Growth rate	110-280	Stebbing, 1976
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (10 g/kg salinity)	3	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (15 g/kg salinity)	5.6	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (20 g/kg salinity)	11	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (25 g/kg salinity)	12.4	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (7.5 C)	52	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (10 C)	34	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (15 C)	9	Theede, et al. 1979
Colonial hydroid, *Laomedea loveni*	Cadmium chloride	-	7 days	EC50 (17.5 C)	5.6	Theede, et al. 1979
Polychaete worm, *Capitella capitata*	Cadmium chloride	-	28 days	LC50	630	Reish, et al. 1978
Polychaete worm, *Capitella capitata*	Cadmium chloride	-	28 days	50% mortality	700	Reish, et al. 1976
Polychaete worm, *Neanthes arenaceodentata*	Cadmium chloride	-	28 days	50% mortality	3,000	Reish, et al. 1976
Polychaete worm, *Ophryotrocha labronica*	Cadmium chloride	-	17 days	50% mortality	1,000	Brown & Ahsanullah, 1971
American oyster, *Crassostrea virginica*	Cadmium iodide	-	40 days	BCF = 677	-	Kerfoot & Jacobs, 1976

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result[a] (µg/l)	Reference
American oyster, *Crassostrea virginica*	Cadmium chloride	-	21 days	BCF=149	-	Eisler, et al. 1972
Soft shell clam, *Mya arenaria*	Cadmium chloride	-	7 days	LC50	150	Eisler, 1977
Soft shell clam, *Mya arenaria*	Cadmium chloride	-	7 days	LC50	700	Eisler & Hennekey, 1977
Bay scallop, *Aquipecten irradians*	Cadmium chloride	-	42 days	EC50 growth reduction	78	Pesch & Stewart, 1980
Bay scallop, *Aquipecten irradians*	Cadmium chloride	-	21 days	BCF=168	-	Eisler, et al. 1972
Common mussel, *Mytilus edulis*	Cadmium EDTA	-	28 days	BCF=252	-	George & Coombs, 1977
Common mussel, *Mytilus edulis*	Cadmium alginate	-	28 days	BCF=252	-	George & Coombs, 1977
Common mussel, *Mytilus edulis*	Cadmium humate	-	28 days	BCF=252	-	George & Coombs, 1977
Common mussel, *Mytilus edulis*	Cadmium pectate	-	28 days	BCF=252	-	George & Coombs, 1977
Common mussel, *Mytilus edulis*	Cadmium chloride	-	21 days	BCF=710	-	Janssen & Scholz, 1979
American lobster, *Homarus americanus*	Cadmium chloride	-	21 days	BCF=25	-	Eisler, et al. 1972
Copepod, *Tigriopus japonicus*	Cadmium sulfate	-	48 days	Inhibited reproduction	44	D'Agostino & Finney 1974
Mysid shrimp, *Mysidopsis bahia*	-	-	17 days	LC50	11	Nimmo, et al. 1977a
Mysid shrimp, *Mysidopsis bahia*	Cadmium chloride	-	28 days	LC50	16	U.S. EPA, 1980

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Mysid shrimp, *Mysidopsis bahia*	Cadmium chloride	-	8 days	LC50	60	U.S. EPA, 1980
Mysid shrimp, *Mysidopsis bigelowi*	Cadmium chloride	-	8 days	LC50	70	U.S. EPA, 1980
Mysid shrimp, *Mysidopsis bigelowi*	Cadmium chloride	-	28 days	LC50	18	U.S. EPA, 1980
Isopod, *Idotea baltica*	Cadmium sulfate	-	5 days	LC50 (3 g/kg salinity)	10,000	Jones, 1975
Isopod, *Idotea baltica*	Cadmium sulfate	-	3 days	LC50 (21 g/kg salinity)	10,000	Jones, 1975
Isopod, *Idotea baltica*	Cadmium sulfate	-	1.5 days	LC50 (14 g/kg salinity)	10,000	Jones, 1975
Isopod, *Jaera albifrons*	Cadmium sulfate	-	5 days	LC50 (3.5 g/kg salinity)	10,000	Jones, 1975
Isopod, *Jaera albifrons*	Cadmium sulfate	-	5 days	LC10 (35 g/kg salinity)	10,000	Jones, 1975
Pink shrimp, *Penaeus duorarum*	Cadmium chloride	-	30 days	LC50	720	Nimmo, et al. 1977b
Grass shrimp, *Palaemonetes vulgaris*	Cadmium chloride	-	29 days	LC50	120	Nimmo, et al. 1977b
Grass shrimp, *Palaemonetes pugio*	Cadmium chloride	-	42 days	LC50	300	Pesch & Stewart, 1980
Grass shrimp, *Palaemonetes pugio*	Cadmium chloride	-	21 days	LC25 (5 g/kg salinity)	50	Vernberg, et al. 1977
Grass shrimp, *Palaemonetes pugio*	Cadmium chloride	-	21 days	LC10 (10 g/kg salinity)	50	Vernberg, et al. 1977
Grass shrimp, *Palaemonetes pugio*	Cadmium chloride	-	21 days	LC5 (20 g/kg salinity)	50	Vernberg, et al. 1977

Table 6. (Continued)

Species	Chemical	Hardness mg/l $(CaCO_3)$	Duration	Effect	Result* (µg/l)	Reference
Grass shrimp, Palaemonetes pugio	Cadmium chloride	-	6 days	LC75 (10 g/kg salinity)	300	Middaugh & Floyd, 1978
Grass shrimp, Palaemonetes pugio	Cadmium chloride	-	6 days	LC50 (15 g/kg salinity)	300	Middaugh & Floyd, 1978
Grass shrimp, Palaemonetes pugio	Cadmium chloride	-	6 days	LC25 (30 g/kg salinity)	300	Middaugh & Floyd, 1978
Grass shrimp, Palaemonetes pugio	Cadmium chloride	-	21 days	BCF=140	-	Vernberg, et al. 1977
Blue crab, Callinectes sapidus	Cadmium nitrate	-	7 days	LC50 (10 g/kg salinity)	50	Rosenberg & Costlow, 1976
Blue crab, Callinectes sapidus	Cadmium nitrate	-	7 days	LC50 (30 g/kg salinity)	150	Rosenberg & Costlow, 1976
Mud crab, Rhithropanopeus harrisii	Cadmum nitrate	-	11 days	LC80 (10 g/kg salinity)	50	Rosenberg & Costlow, 1976
Mud crab, Rhithropanopeus harrisii	Cadmium nitrate	-	11 days	LC75 (20 g/kg salinity)	50	Rosenberg & Costlow, 1976
Mud crab, Rhithropanopeus harrisii	Cadmium nitrate	-	11 days	LC40 (30 g/kg salinity)	50	Rosenberg & Costlow, 1976
Fiddler crab, Uca pugilator	-	-	10 days	50% mortality	2,900	O'Hara, 1973
Fiddler crab Uca pugilator	Cadmium chloride	-	-	Effect on respiration	1.0	Vernberg, et al. 1974
Hermit crab, Pagurus longicarpus	Cadmium chloride	-	7 days	25% mortality	270	Eisler and Hennekey, 1977
Hermit crab, Pagurus longicarpus	Cadmium chloride	-	60 days	50% mortality	70	Pesch & Stewart, 1980
Crab (larva), Eurypanopeus depressus	Cadmium chloride	-	8 days	50% mortality	10	Mirkes, et al. 1978

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Rock crab, Cancer irroratus	Cadmium chloride	-	4 days	Enzyme activity	1,000	Gould, et al. 1976
Starfish, Asterias forbesi	Cadmium chloride	-	7 days	25% mortality	270	Eisler & Hennekey, 1977
Herring (larva), Clupea harengus	Cadmium chloride	-	-	100% embryonic survival	5,000	Westernhagen, et al. 1979
Herring (larva), Clupea harengus	Cadmium chloride	-	-	10% viable hatch	560	Westernhagen, et al. 1979
Pacific herring (embryo), Clupea pallasi	Cadmium chloride	-	<1.0 days	17% reduction in volume	10,000	Alderdice, et al. 1979a
Pacific herring (embryo), Clupea pallasi	Cadmium chloride	-	4 days	Decrease in capsule strength	1,000	Alderdice, et al. 1979b
Pacific herring (embryo), Clupea pallasi	Cadmium chloride	-	2 days	Reduced osmolality of perivitelline fluid	1,000	Alderdice, et al. 1979c
Striped bass (juvenile), Morone saxatilis	Cadmium choride	-	90 days	Significant decreae in enzyme activity	5	Dawson, et al. 1977
Striped bass (juvenile), Morone saxatilis	Cadmium chloride	-	30 days	Significant decrease in oxygen consumption	0.5-5.0	Dawson, et al. 1977
Spot (larva), Leiostomus xanthurus	Cadmium chloride	-	9 days	Incipient LC50	200	Middaugh, et al. 1975
Cunner (adult), Tautogolabrus adspersus	Cadmium chloride	-	60 days	37.5% mortality	100	MacInnes, et al. 1977
Cunner (adult), Tautogolabrus adspersus	Cadmium chloride	-	30 days	Depressed gill tissue oxygen consumption	50	MacInnes, et al. 1977
Cunner (adult), Tautogolabrus adspersus	Cadmium chloride	-	4 days	Decreased enzyme activity	3,000	Gould & Karolus, 1974

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Juvenile mullet, *Aldrichetta forsteri*	Cadmium chloride	-	5 days	50% mortality	14,300	Negilski, 1976
Atlantic silverside, *Menidia menidia*	Cadmium chloride	-	19 days	LC50 (12 g/kg salinity)	<160	Voyer, et al. 1979
Atlantic silverside, *Menidia menidia*	Cadmium chloride	-	19 days	LC50 (20 g/kg salinity)	540	Voyer, et al. 1979
Atlantic silverside, *Menidia menidia*	Cadmium chloride	-	19 days	LC50 (30 g/kg salinity)	>970	Voyer, et al. 1979
Mummichog (adult), *Fundulus heteroclitus*	Cadmium chloride	-	2 days	LC50 (20 g/kg salinity)	60,000	Middaugh & Dean, 1977
Mummichog (adult), *Fundulus heteroclitus*	Cadmium chloride	-	2 days	LC50 (30 g/kg salinity)	43,000	Middaugh & Dean, 1977
Mummichog, *Fundulus heteroclitus*	Cadmium chloride	-	21 days	BCF=48	-	Eisler, et al. 1972
Mummichog (larva), *Fundulus heteroclitus*	Cadmium chloride	-	2 days	LC50 (20 g/kg salinity)	32,000	Middaugh & Dean, 1977
Mummichog (larva), *Fundulus heteroclitus*	Cadmium chloride	-	2 days	LC50 (30 g/kg salinity)	7,800	Middaugh & Dean, 1977
Atlantic silverside (adult), *Menidia menidia*	Cadmium chloride	-	2 days	LC50 (30 g/kg salinity)	12,000	Middaugh & Dean, 1977
Atlantic silverside (adult), *Menidia menidia*	Cadmium chloride	-	2 days	LC50 (20 g/kg salinity)	13,000	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	Cadmium chloride	-	2 days	LC50 (20 g/kg salinity)	2,200	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	Cadmium chloride	-	2 days	LC50 (30 g/kg salinity)	1,600	Middaugh & Dean, 1977

Table 6. (Continued)

Species	Chemical	Hardness mg/l ($CaCO_3$)	Duration	Effect	Result* (µg/l)	Reference
Winter flounder, Pseodopleuronectes americanus	Cadmium chloride	-	8 days	Viable hatch - 50%	300	Voyer, et al. 1977
Winter flounder, Pseudopleuronectes americanus	Cadmium chloride	-	60 days	Increased gill tissue respiration	5	Calabrese, et al. 1975

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* Results are expressed as cadmium, not as the compound.

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

Over 50 years have now passed since the first fatal case of acute industrial cadmium poisoning was reported (Legge, 1924) by the British Factory Inspectorate. During the ensuing decades attention was primarily paid to further cases of acute cadmium poisoning occuring via inhalation in industry or through ingestion (Frant and Kleeman, 1941). Harriet Hardy (Hardy and Skinner, 1947) was among the first to suggest significant chronic effects when she reported five cases of ill health in cadmium exposed workmen who had symptoms of anemia and respiratory complaints. The first definitive reports of chronic effects were those of Friberg (1948a,b) who clearly identified emphysema and renal damage among male workers exposed to cadmium oxide dust in a Swedish alkaline battery factory. That cadmium might be associated with health effects as a result of general environmental pollution was gradually recognized during the 1960's as various investigators examined facets of the endemic disease complex called itai-itai in Toyama Prefecture, Japan (Friberg, et al. 1974). These and other reports have spawned a vast literature which now defies concise summarization. Nonetheless, a significant number of excellent general reviews have appeared in recent years and serve as guides to the more significant papers in the scientific literature (Friberg, et al. 1974; Flick, et al. 1971; Kendrey and Roe, 1969; Nordberg, 1974; Fleischer, et al. 1974; Buell, 1975; Perry, et al. 1976; Fassett, 1975; Webb, 1975; U.S. EPA, 1975a,b; National Academy of Science (NAS), 1977).

EXPOSURE

The major nonoccupational routes of human cadmium exposure are through food and tobacco smoke. Data published by the Food and Drug Administration (FDA, 1974) based on market basket surveys over 7 years, show that the average cadmium intake of 15- to 20-year-old males is 39 µg/day, which includes that found in water. If this figure is adjusted by the recommended daily calorie intake for various age groups, the average daily cadmium intake from birth to age 50 is 33 µg/d for men and 26 µg/d for women. More recent domestic data based on fecal excretion give intake figures of 18 µg/d and 21 µg/d for teen-age males residing in Dallas, Texas, (Kjellstrom, 1978) and Chicago, Illinois (Pahren and Kowal, 1978), respectively. The data in Table 1 indicate that the daily intake of cadmium via food for individuals living in the United States is comparable to that in other parts of the world.

Cadmium is concentrated by certain food crop classes to an appreciable extent. In particular, potatoes, root crops, and leafy vegetables show the greatest tendency in this regard and their cadmium content depends to a high degree on the soil solution concentration of the element (Pahren, et al. 1978). Municipal sewage sludges, containing high levels of cadmium of industrial origin and applied to agricultural lands as fertilizer, are potentially important sources of cadmium entry into the human food chain (Counc. Agric. Sci. Tech., 1976). To date there have been no occurrences of cadmium toxicity in animals or man attributed solely to direct

TABLE 1

Daily Cadmium Intake Via Food

Country	µg/day	Reference
United States	39	Food and Drug Administration, 1974
Canada	52	Kirkpatrick and Coffin, 1977
West Germany	48	U.S. EPA, 1975b
Rumania	38-64	U.S. EPA, 1975b
Czechoslovakia	60	U.S. EPA, 1975b
Japan (unpolluted area)	59	U.S. EPA, 1975b
Sweden	17	Kjellstrom, et al. 1978a
Australia	30-50	Miller, et al. 1976
New Zealand	21-27	Guthrie and Robinson, 1977

consumption of vegetation grown on land amended with municipal sludge (Garrigan, 1977). The widespread usage of phosphate fertilizers, most of which contain significant amounts of cadmium (U.S. EPA, 1975a), is potentially a more important source of cadmium entry into human foodstuffs and will ultimately increase the amount of cadmium in the diet.

Balanced diets generally contain levels of cadmium approximating 0.05 mg/kg (Nordberg, 1974). Aquatic food species including fish, crabs, oysters, and shrimps bioconcentrate cadmium, as do visceral meats (liver, kidney, pancreas). Cadmium content depends on the age of animals at slaughter, older animals having higher concentrations (Kreuzer, et al. 1976; Nordberg, 1974).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of cadmium which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals is similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Bioconcentration factors are available for the edible portion of many species of fish and shellfish (Table 2).

The geometric mean of the values available for bivalve molluscs is 444 whereas that for all other species is 11. If the values of 444 and 11 are used with the consumption data, the weighted average bioconcentration factor for cadmium and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 64.

Tobacco in all its forms contains appreciable amounts of cadmium. Since the absorption of cadmium from the lung is substantially greater than that from the gastrointestinal tract, smoking contributes significantly to total body burdens. American cigarettes (Menden, et al. 1972) have been found to contain 1.5 to 2.0 µg per cigarette and about 70 percent of this passes into the smoke (Nandi, et al. 1969). Most data indicate that 0.1 to 0.2 µg cadmium are inhaled for each cigarette smoked. Thus, smoking 20 cigarettes per day will result in the inhalation of about 3 µg per day of cadmium or an absorption of 0.75 µg per day (assuming 25 percent absorption). It has been pointed out that workers handling cadmium compounds may contaminate their cigarette or pipe tobacco and further augment the high metal load contributed by smoking (Piscator, et al. 1976).

Ambient air is not a significant source of cadmium exposure for the vast majority of the United States population. Data from the National Air Sampling Network have been summarized by Tabor and Warren (1958) and Schroeder (1970). Data collected in 1966 in 58 urban and 29 nonurban areas showed a range of concentrations of

TABLE 2

BCFs for Some Species of Fish and Shellfish

Species	BCF	Reference
Brook trout, Salvelinus fontinalis	3	Benoit, et al. 1976
Brook trout, Salvelinus fontinalis	151	Benoit, et al. 1976
Brook trout, Salvelinus fontinalis	10	Sangalang & Freeman, 1979
American oyster, Crassostrea virginica	677	Kerfoot & Jacobs, 1976
American oyster, Crassostrea virginica	2,600	Zaroogian & Cheer, 1976
American oyster, Crassostrea virginica	1,830	Zaroogian, 1979
American oyster, Crassostrea virginica	149	Eisler, et al., 1972
American oyster, Crassostrea virginica	1,220	Schuster & Pringle, 1969
Soft shell clam, Mya arenaria	160	Pringle, et al. 1968
Quahaug, Mercenaria mercenaria	83	Kerfoot & Jacobs, 1976
Bay scallop, Aquipecter irradians	168	Eisler, et al., 1972
Bay scallop, Aquipecter irradians	2,040	Pesch & Stewart, 1980
Common mussel, Mytilus edulis	113	George & Coombs, 1979
Crab, Carcinus maenas	5	Wright, 1977
Crab, Carcinus maenas	7	Jennings & Rainbow, 1979

2-370 and 0.4-26 ng per cubic meter, respectively. The data emphasize that nearly all airborne cadmium is due to man's activities. Highest concentrations are consistently found in industrialized cities and in the vicinity of smelting operations (Fleischer, et al. 1974). In areas where there are no such sources of airborne cadmium pollution the levels observed have generally been around 0.001 $\mu g/m^3$, which leads to an average inhaled amount of approximately 0.02 - 0.03 ug per day for adults. In those cities with the highest levels of cadmium air pollution (up to approximately 400 ng/m^3) the maximum amount inhaled could rise on extreme occasions to 8.0 ug per day. As controls on emissions continue to tighten, intake via the respiratory route is expected to diminish.

Drinking water also contributes relatively little to the average daily intake. A survey of 969 U.S. community water supply systems, representing 5 percent of the national total, revealed an average cadmium concentration of 1.3 µg/l. Only three systems exceeded concentrations of 10 µg/l. Of 2,595 distribution samples taken during this same survey (McCabe et al., 1970) only four samples exceeded the 10 µg/l standard with the maximum sample having a concentration of 0.11 mg/l. Apparently an occasional water source is aggressive enough to cause some dissolution of metal from distribution piping, i.e., galvanized pipe. Most analyses of sea waters have reported average concentrations of 0.1 -0.15 µg/l (Fleischer, et al. 1974). Since this is less than fresh water sources entering the sea and far below the levels expected from solubility factors it has been suggested that cadmium is effectively removed by co-precipitation with or adsorption on clays, hydrous manganese oxide, or phosphorites (Posselt, 1971). Based on the above community water supply study and an average adult consumption rate of 2 l/d, drinking water sources probably contribute not more than 3 - 4 µg/d to the total average cadmium intake.

Very little is known concerning the absorption of cadmium compounds through the skin and only the chloride salt has been studied (Skog and Wahlberg, 1964; Wahlberg, 1965). Maximum absorption of 1.8 percent over 5 hours was observed when a cadmium concentration of 26 gm/l was applied. At lower concentrations, less than 1 percent absorption occurred. Since these levels are higher by a factor of approximately 20 million than household waters used for washing or bathing there seems to be virtually no risk of significant absorption through the skin. However, it should be pointed out that human studies have apparently not been done. Wastewater may indirectly play a considerably greater role since cadmium may enter the food chain from contaminated water used to irrigate fields producing crops for human consumption.

PHARMACOKINETICS

While ingestion constitutes the major part of human intake only a small proportion, i.e., approximately 5 percent, is absorbed, the rest passing directly into the feces. Gastrointestinal absorption is influenced by a number of dietary factors. Diets low in calcium lead to significantly higher levels of absorption and deposition of cadmium into intestinal mucosa, liver, and kidneys (Washko and Cousins, 1976) and corresponding decreases in fecal excretion. Cadmium increases the urinary excretion of calcium without affecting the excretion of phosphorus (Itokawa, et al.

1978). Cadmium inhibits the in vitro uptake of calcium from the rat duodendum, but calcium was not shown to have an inhibitory effect on the in vitro uptake of cadmium (Hamilton and Smith, 1978). While confirming the in vitro inhibitory effect of cadmium on intestinal calcium absorption it has been recently demonstrated that the in vivo treatment of rats with cadmium, either acutely or chronically, does not decrease intestinal calcium absorption (Yuhas, et al. 1978). Diets deficient in vitamin D lead to increased cadmium absorption (Worker and Migicovsky, 1961). Low protein diets also lead to considerably higher levels of cadmium in various organs irrespective of the calcium content of the diet (Suzuki, et al. 1969). Similarly, deficiencies of zinc, iron, and copper have been shown to enhance cadmium uptake and subsequent adverse effects (Banis, et al. 1969; Bunn and Matrone, 1966; Hill, et al. 1963). Ascorbic acid deficiency also promotes cadmium toxicity (Fox and Fry, 1970). The complex relationships between cadmium and various heavy metals and nutrients has been reviewed by Bremner (1974).

Human studies using ^{115m}Cd given orally have yielded absorption values of 6 percent (range 4.7 - 7.0 percent) and 4.6 (range 0.7 - 15.6 percent) (Rahola, et al. 1973; McLellan, et al. 1978). In the latter study, total body counting was used to determine cadmium absorption in 14 healthy subjects aged 21-61 years. A trivalent chromium ($CrCl_3$) marker, which is poorly absorbed from the gastrointestinal tract, was given along with ^{115m}Cd, assuming that unabsorbed cadmium would have the same transit time as chromium. The average body retention of radiocadmium determined between 7 and

14 days after the disappearance of the chromium marker from the body was 4.6 percent with a standard deviation of ± 4 percent. Various animal experiments have usually given lower oral absorption figures, i.e., approximately 2 percent, for ingested cadmium (Friberg, et al. 1974).

In contrast to ingestion, a relatively large proportion of respired cadmium is absorbed and inhalation represents a major mode of entry into the body for smokers and occupationally exposed persons. The fate of inhaled cadmium, in common with other respirable pollutants, depends upon particle size, solubility, and lung status. When a large proportion of particles are in the respirable range and the compound is relatively soluble, 25 percent of the inhaled amount may be absorbed. Cadmium fumes may have an absorption of up to 50 percent and it is estimated that up to 50 percent of cadmium in cigarette smoke may be absorbed (World Health Organization (WHO) Task Group, 1977; Elinder, et al. 1976). Retrograde movement of particulate cadmium due to mucociliary transport may lead to eventual swallowing and gastrointestinal tract absorption.

Most studies on the transport and tissue distribution following absorption have been done in animals. Following intravenous or intraperitoneal administration most of the cadmium is initially found in the blood plasma. After 12-24 hours the plasma is cleared and most of the cadmium has entered erythrocytes which contain the metal-binding protein, metallothionein. With repeated administration the red cell content becomes many times greater than the plasma. Further distribution within the body is dependent on the elapsed time since absorption (U.S. EPA, 1975b).

Irrespective of the route of entry, cadmium is principally stored in the liver and kidneys with higher levels initially found in the liver. Following single exposures, relocation occurs and liver concentrations eventually are exceeded by the renal cortex. Repeated exposures result in eventual high concentrations in both organs. Continued exposure eventually leads to a level of about 200-300 mg/kg wet weight in the renal cortex, after which pathologic changes occur which result in increased excretion of cadmium and protein in the urine, and no further accumulation occurs (WHO Task Group, 1977). The accumulation in the liver and kidneys seems to be mainly dependent on the storage of cadmium in association with the cadmium-binding protein, metallothionein (Chen, et al. 1975; Nordberg, et al. 1975).

Cadmium, unlike many trace metals, has no known function in normal metabolic processes. Recently there has been some speculation that cadmium may be an essential trace element. It has been reported that cadmium deficient animals respond with significant growth effects when cadmium salts are added to a basal diet. These effects are said to be dose-dependent, consistent, and reproducible. In addition, glucose-6-phosphatase dehydrogenase may be activated by cadmium (Cadmium Research Digest, 1977). Confirmation of these findings, while of great scientific interest, would not lessen the need to control potential toxic exposures to the element. The factor which makes cadmium contamination of the environment a particularly serious hazard from the human health standpoint, is its pronounced tendency to bioaccumulate. Elinder and Kjellstrom (1977) have compared renal cadmium levels in specimens taken in recent autopsies (57 µg/gm dry weight) with specimens collected in the last century (15 µg/gm dry weight). These data indicate that cadmium body burdens are increasing, perhaps reflecting increased general environmental exposure to the element. A review of a great number of studies indicates that the total body burden of cadmium in humans increases with age, (Friberg, et al. 1974) from very minimal levels at birth ($<$ 1 µg), (Henke, et al. 1970) to an average of up to 30-40 mg by the age of 50 in nonoccupationally exposed individuals (Friberg, et al. 1974). About 75 percent of this accumulation is found in the kidneys and liver, the kidneys containing approximately one-third of the average body burden with the highest levels localized in the renal cortex. In general, the liver continues to concentrate cadmium until the late decades of life while kidney concentrations increase to the fourth decade, peak, and steadily decline from the sixth decade (Gross, et al. 1976). The pancreas and salivary glands also contain considerable concentrations of cadmium while the brain and bone acquire only very small quantities (Nordberg, 1974). Age appears to have significant effects on how cadmium distributes after absorption. Using $^{115m}CdCl_2$ in rats, Kello and Kostial (1977) demonstrated that cadmium whole body retention declined with increasing age. Young animals had disproportionately more cadmium in their kidney and blood than older animals and correspondingly less accumulation in the liver. Smokers have an appreciably greater body burden of cadmium than nonsmokers. The average concentration in the renal cortex is approximately doubled in smokers (Elinder, et al. 1976; Hammer, et al. 1973). It is of interest that in Japan where the average diet contains appreciably more cadmium than in Western countries, the metal could be detected in 57 percent of human embryos of 31 to 35 days gestation and this figure increased to 80 percent during the second trimester (Chaube, et al. 1973). Blood levels in newborn babies are correlated with maternal blood levels, but average only 50 percent of the maternal levels (Lauwerys, et al. 1978). In environmentally exposed children, urinary cadmium levels were a more sensitive indicator of exposure than blood cadmium (Roels, et al. 1978).

In nonoccupationally exposed persons the mean level of cadmium in the blood is usually less than 1 µg/100 ml. Children without known exposure, aged 2 months to 13 years (average 4.9 years), are reported as having slightly lower levels, i.e., 0.66 µg/100 ml (Smith, et al. 1976). Smokers are reported as having blood cadmium levels 50 percent greater than nonsmokers (Einbrodt, et al. 1976).

Several reports indicate that urinary excretion of cadmium is approximately 1-2 µg/day in the general population (Imbus, et al. 1963; Szadkowski, et al. 1969). There is a modest increment in urinary levels with age (Katagiri, et al. 1971). Urinary excretion may be markedly elevated in exposed workers including those without renal damage (Friberg, et al. 1974). If renal tubular dysfunction should occur due to cadmium accumulation, the rate of urinary cadmium excretion will further increase, which in turn results in a considerable decrease in renal cadmium levels, even though irreversible tubular damage has already occurred (Kjellstrom, 1976). It should be mentioned that renal levels fall after age 50 even in "normal" persons and decreased renal levels are not necessarily due to cadmium-induced renal disease.

Fecal excretion appears to closely reflect the dietary intake (Tipton and Stewart, 1970; Kojima, et al. 1977) as might be anticipated from the previously discussed absorption data. Smokers have a slightly increased fecal excretion rate averaging 3.2 µg/d (Kjellstrom, et al. 1978a). It is unknown how much fecal cadmium may be derived from intestinal epithelium or biliary excretion. Saliva contains up to 0.1 µg/g cadmium (Driezen, et al. 1970) and may contribute significantly to fecal excretion since a normal adult will secrete 1,000-1,500 ml/d. The amount of gastrointestinal reabsorption is unknown. Biliary excretion has been studied by Stowe (1976) who observed normal rat bile to contain 22 ± 3 ppb cadmium. Rats fed 100 ppm cadmium excreted bile containing 58 ± 6 ppb. Less than 0.1 percent of subcutaneously-injected cadmium was excreted in the bile within the first 5 hours following administration.

Hair is a minor excretory pathway and may contain from 0.5 to 3.5 µg/g (Friberg, et al., 1974). In rats, continued exposure to cadmium in drinking water leads to initially high hair levels, which decline dramatically with continued administration. It has been concluded that hair cadmium would not be useful in estimating either concentrations in vital organs or degree of organ damage (Brancato, et al. 1976). In infancy human hair has been shown to have relatively high levels of cadmium which thereafter decline throughout life (Gross, et al. 1976). While positive correlations have been reported between environmental levels (Hammer, et al. 1971) and occupational exposure and visceral organ levels (Oleru, 1975) these associations are generally too weak to permit accurate quantitative assessments of human exposure to cadmium.

Estimates of the biologic half-time of absorbed cadmium have been derived in a number of ways, i.e., by theoretical metabolic balance studies, determining the half-time in blood or urine, and by measuring the decrease in whole-body retention of isotopic cadmium.

Studies on the half-time in urine (Sudo and Nomiyama, 1972) or blood (Tsuchiya, 1970) have given values of 200 days and 1 year, respectively, for former occupationally-exposed workers. The number of workers studied was very small. Obviously, this approach may not reflect the total body burden of cadmium, some of which may be very tightly bound in various tissues. Also, these subjects are not representative of normal environmental exposure in which urine may reflect the total body burden (Tsuchiya, et al. 1976), but of current exposure when such exposure has been or is high (Lauwerys, et al. 1976). Blood also is thought to best represent current exposure (Lauwerys, et al. 1976). Direct comparison of urinary excretion levels and estimated body burden have also been performed using Japanese, American, and German data. These data suggest a half-time of 13-47 years. Similar time frames have been found using more complex metabolic models and Friberg (Friberg, et al. 1974) has concluded that the biologic half-time is probably 10-30 years. These methods suffer the disadvantage that actual body burdens cannot be ascertained for the living subject and are assumed to be the same as averages derived from autopsy studies.

Only two human studies using radioisotopes are available. Rahola, et al. (1973) stated it was not possible to accurately determine a biologic half-time, but provided a shortest estimate of 130 days and a longest of infinity. In a single human subject for whom the figure could be calculated the biologic half-time was 100 days (McLellan, et al. 1978).

From the foregoing, it is obvious that the data are not in good agreement regarding cadmium half-time with estimates varying at least 100-fold (months v. decades). Since this is a critical issue in terms of maximum daily limits for standard-setting purposes, it is essential that more new data be generated to resolve this facet of cadmium metabolism. Nomiyama, et al. (1978) has demonstrated in Rhesus monkeys that cadmium half-time is inversely related to the oral intake of the element. This may explain some of the wide variation seen in human studies.

In summary, from the exposure, intake, absorption, and excretion data it appears that most persons exposed to cadmium in the general environment are in an approximate cadmium balance. Autopsy data suggest a slight positive balance until approximately age 50 after which a negative balance ensues. The reasons for this decline are unknown. It is unrelated to the presence or absence of renal disease, but may be due to the lessened intake of food as caloric needs also decline in later life. It has also been suggested that the observed decrease may be an artifact related to the possibility that older persons have been exposed to far lower cadmium levels during their youth (Hammer, et al. 1973).

EFFECTS

Acute, Subacute, and Chronic Toxicity

When adminstered orally, cadmium acts as an emetic in both man and subhuman species. Cadmium metal is quite soluble in weak acids such as those commonly found in many foods and beverages. Organic cadmium salts may be transformed upon contact with gastric hydrochloric acid into cadmium chloride which has an inflammatory action on the mucus membranes of the stomach and intestine (Browning, 1969). Oral administration of cadmium produces emesis at a concentration of about 400 ppm (23 mg/kg) in food (Schwarze and Alsberg, 1923). These authors cite the case of Burdach, who induced vomiting with one-half grain of cadmium sulfate, which contains about 15 mg of cadmium.

The oral LD_{50} in rats varies only slightly with the cadmium compound employed, i.e., oxide, 72 mg/kg; chloride, 88 mg/kg; and fluorosilicate, 100 mg/kg. The lowest oral dose producing death in rats using cadmium fluroborate has been given as 250 mg/kg. The LD_{50} for guinea pigs given cadmium fluoride is reported to be 150 mg/kg (National Institute for Occupational Safety and Health (NIOSH), 1974). More complete acute toxicity data are given in an U.S. EPA report (U.S. EPA, 1975a). The lethal oral dose of cadmium for man is not known (Thienes and Haley, 1972).

Because of its acid solubility and formerly widespread usage in plating metal utensils and containers, cadmium has been responsible for numerous outbreaks of acute poisoning in the past. Some 689 cases of cadmium poisoning were reported within the 5-year period 1941-1946 (Fairhall, 1957) and doubtless numerous other undiagnosed and unreported cases also occurred. Largely as a result of these outbreaks various sanitary codes and national standards have been amended to prohibit the use of cadmium in any article used for food or drink preparation or storage. The most significant clinical feature of acute cadmium poisoning is the rapidity with which symptoms become apparent following ingestion. Most persons become symptomatic within 15 to 30 minutes after ingesting either food or drink containing toxic amounts of the metal. The symptoms typically include persistent vomiting, increased salivation, choking sensations, abdominal pain, tenesmus, and diarrhea (Browning, 1969; Frant and Kleeman, 1941). The dose causing such symptoms has been estimated to be within the range of 15-30 mg (Gleason, et al. 1969; Nordberg, 1974).

Because numerous cases of acute industrial poisoning from cadmium have occurred from dust or fume generated by the burning, heating, welding, melting, or pouring of cadmium metal, cadmium alloys, or cadmium plate, the respiratory tract effects have been well documented (Kazantzis, 1963).

Symptoms from acute poisoning by cadmium oxide fumes appear 4-6 hours after exposure and include cough, shortness of breath and tightness of the chest. Pulmonary edema may ensue within 24 hours, often to be followed by bronchopneumonia. Most cases are resolved within a week. The fatality rate ranges between 15 and 20 percent (Bonnell, 1965). Later effects from acute overexposure include pulmonary fibrosis (Health, et al. 1968), permanently impaired lung function (Townshend, 1968) and disturbed liver function (Blejer, et al. 1971). Barrett and Card (1947) estimated that the lethal dose for a man doing light work would not exceed 2,900 minutes mg/m^3. From these figures it may be estimated that a lethal exposure to cadmium fume may result from breathing a concentration of approximately 5 mg/m^3 over an 8-hour period. In Blejer's fatal case it was thought that the atmospheric concentration exceeded 1 mg/m^3.

Ansomia is a well described defect in those employed in the cadmium industry and correlates with the appearance of proteinuria, i.e., both depend upon length of service (Potts, 1965; Friberg, 1950; Adams and Crabtree, 1961; Tsuji, et al. 1972). Pihl and Parkes (1977) noted elevated cadmium and lead levels in the hair of children with learning disability.

A host of chronic effects attributed to cadmium exposure have been reported by numerous investigators over the past three decades. Without doubt, at least in terms of human effects, the two cardinal pathologic lesions associated with cadmium are pulmonary emphysema and renal tubular damage.

Friberg (1948a,b; 1950) was the first to note emphysema in his now classic studies of workers exposed to cadmium iron oxide dust in a Swedish alkaline battery factory. Since then numerous investigators have confirmed and expanded upon these initial findings (Paterson, 1947; Baader, 1952; Lane and Campbell, 1954; Buxton, 1956; Smith, et al. 1960; Kazantzis, et al. 1963; Potts, 1965; Holden, 1965; Lewis, et al. 1969; Snider, et al. 1973; Lauwerys, et al. 1974; Smith, et al. 1976).

A possible mechanism for cadmium emphysema has been suggested by Chowdbury and Lauria (1976) who noted that the addition of cadmium to human plasma caused an inhibition of alpha-1-antitrypsin with a decrease in trypsin inhibitory capacity. Other metals had little or no effect at equimolar concentrations. Persons with congenital alpha-1-antitrypsin deficiency have a marked increased risk of emphysema and cadmium may stimulate or augment this defect.

Based on data from studies of the acute pulmonary effects, the studies of long-term industrial exposure, and the absence of contradicting animal data it seems apparent that cadmium induced emphysema is related only to the inhalation route of exposure. Apparently no studies have been done relating the incidence of emphysema in the general population to varying ambient levels of airborne cadmium.

There is general agreement that renal tubular damage is the most important chronic effect of cadmium exposure irrespective of route. The hallmark of this injury is the appearance of a low molecular weight (20,000-25,000) protein in the urine (B_2-microglobulin). Industrial studies have shown that proteinuria is not only much more common than emphysema, but also that it appears after shorter periods of exposure. This protein is not the same as that excreted after conventional kidney damage and doesn't react in the usual laboratory tests designed to detect urinary protein (Browning, 1969). First reported in 1948 by Friberg in workers exposed to cadmium oxide dust, B_2-microglobulin has subsequently been reported in the urine of workers exposed to other forms of cadmium and in the urine of animals experimentally exposed. As cadmium accumulates in the kidney it inhibits tubular reabsorption resulting in proteinuria (Berggard and Bearn, 1968). Other signs of renal tubular dysfunction resulting from cadmium exposure are glycosuria, aminoaciduria, and changes in the metabolism of calcium and phosphorus (Kazantzis, 1963). The dysfunction rarely progresses to renal failure, but hypercalcinuria may occasionally lead to a negative calcium balance and to osteomalacia (Nicaud, et al. 1942; Adams, et al. 1969).

High levels of proteinuria have been found in itai-itai disease patients where increased excretion is strongly correlated to residence time in exposed areas and the use of cadmium contaminated river water (Kjellstrom, et al. 1977). Tsuchiya, et al. (1978) has found that B_2-microglobulin excretion is highly correlated with aging in both high and low cadmium exposure population groups. Kjellstrom has attempted to determine a dose response between B_2-microglobulin excretion and cadmium in air (Kjellstrom, 1977a,b; Kjellstrom, et al. 1977). He determined the geometric average B_2-microglobulin concentration to be 84 µg/l in normal unexposed persons with 95 percent confidence limits of 24-290 µg/l. Using the upper 95 percent limit he found an elevated excretion prevalence of 19 percent for workers with 6-12 years exposure. Smokers were also noted to have about 2 to 3 times the prevalence of elevated excretion found for nonsmokers. This applies to both the industrially-exposed smokers as well as non-exposed workers. Women are noted to have a lower prevalence than men and this is attributed to sex differences in smoking habits.

Kjellstrom, et al. (1977) is careful to point out that elevated chronic excretion of B_2-microglobulin does not equate with clinically significant proteinuria and that its definition was designed for comparative epidemiological purposes. While pointing out that the relationship of cadmium proteinuria to life expectancy is unknown, Kazantzis (1977) believes it is evidence of a critical effect. Adams, et al. (1969) long-term observations indicate that some men have had proteinuria for many years without serious impairment of kidney function. He notes that retired men do not seem to have more serious renal disease than those still at work and that there is no good evidence of progression to terminal renal failure. On occasion the renal lesion may be severe enough to produce osteomalacia and multiple fractures as in itai-itai disease. However, in all such cases (Friberg, et al. 1974; Nicaud, et al. 1942; Adams, et al. 1969) there appears to have been multiple dietary deficiencies (calcium, protein, Vitamin C, Vitamin D) in addition to an excessive cadmium exposure. For example, itai-itai disease occurs almost exclusively in grand multiparous women over the age of 50 who live predominantly on a rice diet with a high (up to 600 µg/d) cadmium content. The Japanese government has monitored for new cases of itai-itai disease since 1969. Since then no new patients with the disease have been found, although the frequency of tubular dysfunction and urinary cadmium are higher in polluted than in control areas (Shigematsu and Yoshida, 1978). Nicaud's cases occurred under wartime factory conditions in France. It seems apparent that multiple nutritional deficiencies may be more important than cadmium in producing this complex disorder. While the bone changes (osteomalacia) have been assumed to be secondary to the renal defect, it has been shown in animals that cadmium may directly cause osteoporotic bone changes (Yoshiki, et al.

1975). Such evidence implies that certain segments of the population living on subsistence diets may well be at increased risk from cadmium.

Based on animal and limited human data, the critical cadmium concentration in the renal cortex has been estimated to be about 200 mg/kg wet weight (WHO Task Group, 1977; Friberg, et al. 1974; Nordberg, 1976). The 28 human cases used to support this figure show an extremely large variation in concentration. Nomiyama (1977) points out that this figure should be determined from data in cases where proteinuria was the only finding, i.e., excluding those cases with obvious pathologic changes since in long standing severe disease the net amount of cadmium may be decreased from that at disease inception. In the eight cases with proteinuria only, the concentration varied from 150 to 395 mg/kg wet weight with the exception of a single specimen with a level of 21 mg/kg wet weight. Four had levels in excess of 300. He suggests that 300 mg/kg wet weight is a more appropriate critical level. This is supported by his findings on monkeys (Nomiyama, et al. 1977).

Kjellstrom (1977a,b) has used the figure of 200 mg/kg wet weight of cadmium in the renal cortex as an estimate of the level where tubular damage occurs in constructing a metabolic model from which to calculate a dose-response corresponding to daily intake. His model gives lower values for Japanese than Europeans because of the former's smaller average body and kidney weight. For Europeans the expected response rate, i.e., the proportion of the population with evidence of renal tubular damage, as manifested by excessive B_2-microglobulin excretion for a given daily cadmium intake, is expected to approximate the following sequence: 0.1 percent-32 µg Cd/d; 1.0 percent-60 µg Cd/d; 2.5 percent-80 µg Cd/d; 5.0 percent-100 µg Cd/d; 10 percent-148 µg Cd/d; and 50 percent-440 µg Cd/d. These estimates are for nonsmokers. Smoking will reduce the above allowable intake from food by approximately 25 µg/d for each package of cigarettes smoked. Water consumption will reduce the allowance for food on a µg for µg basis assuming equilivent gastrointestinal absorption for food and water. Other sources of cadmium would normally have only very minor effects. If the value for renal damage averages closer to 300 mg cadmium/kg wet weight of cortex instead of 200 this would result in a proportional increase in allowable daily intake.

In addition to the generally conceded major toxic effects of cadmium in man it has been hypothesized that exposure to ambient cadmium levels may be an important factor in the etiology of essential hypertension. Three major lines of evidence have been set forth to support this thesis: (1) in some animal experiments cadmium has induced hypertension; (2) hypertension is positively correlated with the ingestion of soft drinking waters, which often contain higher concentrations of heavy metals than hard waters; and (3) hypertension patients have higher renal, bone, and body fluid cadmium levels (Schroeder and Vinton, 1962; Schroeder, 1964a,b, 1965, 1966; Schroeder and Balassa, 1961; Crawford, et al. 1968; Lener and Bibr, 1971; Thind and Fischer, 1976; Crawford, 1973; Perry, 1972). Hypertension is not always found in animals exposed to cadmium (Lener and Bibr, 1971); and this effect shows variability among strains and is related to the amount of sodium chloride in the diet (Nordberg, 1974). In rats, genetic composition is a critical determinant for the induction of hypertension by cadmium. Selective inbreeding has led to animals which are completely resistant to this effect (Ohanian and Iwai, 1978). Most of the studies relating elevated tissue levels of cadmium to hypertension (Schroeder, 1965; Perry and Schroeder, 1955; Thind and Fischer, 1976; Lener and Bibr, 1971; Glauser, et al. 1976) were carried out before the impact of smoking on cadmium accumulation was appreciated, or have tended to ignore this factor. Much careful work now tends to indicate that the association between hypertension and cadmium may be a spurious one. Morgan (1972) in a large autopsy series was unable to correlate hypertension and mean renal cadmium. Similarly, Lewis, et al. (1972) failed to find a relationship between renal levels of cadmium and hypertension. Beevers, et al. (1976) were unable to find any significant differences in blood cadmium between 70 hypertensive patients and 70 controls who were matched for age and sex. Østergaard (1977) compared renal cadmium tissue levels in 39 hypertensive and 43 normotensive subjects. In this series only subjects 45-65 years of age were studied to minimize the effects of age on cadmium accumulation. The data suggest that hypertensive renal disease may enhance cadmium excretion. Szadkowski's (1969) study measured the urinary excretion of cadmium in a large series of persons and could find no relationship between cadmium excretion and hypertension. Very significantly, epidemiologic studies of industrially exposed persons have failed to support the concept that cadmium is a significant factor in human hypertension (Friberg, et al. 1974; Holden, 1969). In addition, Japanese patients with itai-itai disease do not have hypertension (Perry, 1972; Nogawa and Kawana, 1969).

Besides the effects previously discussed, chronic exposure to cadmium has been suggested to play a causative role in a number of other pathologic changes in man. These studies are usually in the form of case reports and often have been reported by only a single author or group. In general, these effects when considered individually are of lesser importance to human health, but collectively represent possibly an important gap in the knowledge concerning cadmium toxicity. A brief discussion of several of the more significant of these adverse effects follows.

Friberg (1950) noted abnormal liver function tests in his classic study first documenting emphysema and kidney damage. Blejer, et al. (1971) also found such changes in cases of acute overwhelming exposure. Other authors have commented upon the rarity of such findings (Bonnell, 1965; Kazantzis, et al. 1963).

Renal stones have been reported for both Swedish and British workers exposed to cadmium (Ahlmark, et al. 1961; Adams, et al. 1969). These have occurred in both proteinuric and nonproteinuric workmen. Since renal stones are a common problem more definitive industry wide studies are needed to determine the true prevalence of this problem.

Moderate anemia has been described in a number of studies (Friberg, 1950; Hardy and Skinner, 1947). This effect is also seen in animals with experimental cadmium poisoning (Prodan, 1932).

Other reported effects include changes in lipids (Schroeder and Balassa, 1965), rhinorrhea (Baader, 1952), bone marrow changes

(Cotter and Cotter, 1951), dental caries (Hardy and Skinner, 1947), and nonspecific nervous system signs and symptoms (Vorobjeva, 1957).

Koller has published a series of papers describing various forms of immunosuppression in experimental animals treated with cadmium, i.e., lower neutralizing titers against pseudorabies virus, decreased antibody synthesis, decreased levels of IgG, etc. (Koller, 1973; Koller, et al. 1975, 1976). In animals, cadmium has been shown to affect various enzymes which control blood glucose levels. The significance of these findings in terms of human health is conjectural.

Synergism and/or Antagonism

A wide range of chemical and natural substances have been shown to modify the toxicologic properties of cadmium. This effect has been seen in highly varying biological systems and appears to be in many instances due to competition with other metallic elements for protein-binding sites.

Cadmium toxicity is decreased by other metal ions. In animals zinc has been shown to prevent cadmium-induced testicular damage and teratogenic effects (Parizek, 1957; Parizek, et al. 1969; Ferm and Carpenter, 1967). It reportedly reduces cadmium's ability to induce tumors (Gunn, et al. 1963a,b; 1964) and it reduces cadmium-induced growth inhibition. Copper has also been shown to reduce mortality and anemia induced by cadmium in various species and to prevent the degenerative effects of cadmium on aortic elastin (Hill, et al. 1963; Bunn and Matrone, 1966). Starcher (1969) has shown that cadmium decreases intestinal copper uptake, probably through competition for binding sites.

The anemia produced experimentally in fowl fed high cadmium diets is remedied by increases in iron or ascorbic acid intake (Hill, et al. 1963; Fox and Fry, 1970; Fox, 1975). The protective effect of these agents may be mediated by increased iron absorption in the intestine (Freeland and Cousins, 1973). The situation seems analogous to copper.

There is mounting evidence that elevated cadmium intake can adversely affect calcium metabolism (Bremner, 1974). Bone disease was first recognized as a toxic manifestion of cadmium during World War II (Nicaud, et al. 1942) and osteomalcia is an important component of itai-itai disease. Two explanations are attractive: (1) that the bone disease is secondary to cadmium induced renal tubular dysfunction or (2) that cadmium accumulation is in part a consequence of diets deficient in calcium and Vitamin D. The latter explanation seems the most appropriate (Larsson and Piscator, 1971). The osteoporotic changes may arise from an inhibitory effect of cadmium on the renal synthesis of 1,25-dihydroxy-cholecalciferol, which is the active form of Vitamin D_3. This inhibition has been demonstrated *in vitro* (Feldman and Cousins, 1973).

Rats which have been pre-treated with cadmium show decreased intestinal absorption of calcium and markedly increased fecal calcium excretion. These animals also demonstrate a 30 percent decrease in calcium incorporation in bone and the investigators suggest these effects are important in the etiology of itai-itai disease (Ando, et al. 1977; Kobayashi, 1970).

The effects of protein in reducing cadmium toxicity have previously been mentioned. It has been suggested that the protective effects are actually due to increased availability of zinc and/or iron (Fox, et al. 1973).

Cadmium itself will induce tolerance if given by small repetitive injections (Nordberg, 1971). This effect is postulated to be due to the stimulation or induction of a protective protein, metallothionein. Probst, et al. (1977) have demonstrated that hepatic metallothionein concentrations increase in proportion to the cadmium pretreatment dose and found a positive correlation between dose related increases in hepatic metallothionein and cadmium LD_{50} values. This cadmium binding protein apparently plays a key role in cadmium detoxication. It contains a high (30) percentage of cysteinyl residues and hence has an extreme affinity for metal binding. About one metal ion is bound per three -SH groups and it may contain up to 9 percent metal. Zinc usually occupies the vast majority of binding sites, but may be replaced by various other cations, i.e., cadmium, cobalt, mercury, copper, etc. The protective effect of prior administration of zinc against cadmium has been attributed to the increased accumulation of hepatic and renal cadmium as metallothionein. The inactivity of cadmium-metallothionein complexes in reducing SH enzyme activity and 1,25-dihydroxy-cholecalciferol synthesis suggests that the bound form is inactive (Webb, 1975; Feldman and Cousins, 1973). As might be anticipated cysteine similarly protects against cadmium induced testicular necrosis (Gunn, et al. 1968a). The synthesis of metallothionein-like proteins can be induced by at least two essential elements, i.e., zinc and copper, and the protein may have a fundamental role in the metabolism of these elements. The induction by cadmium and mercury may therefore simply be a fortunate circumstance occasioned by chemical similarities (Webb, 1972). Beryllium, manganese, barium, strontium, tin, arsenic, selenium, chromium, and nickel administration have been shown not to influence liver or kidney levels of metallothionein-like protein whereas cobalt and iron increase liver levels and bismuth increases renal tissue concentrations (Pitrowski, et al. 1976).

Selenium is yet another protective element which is able to prevent lethal cadmium effects or the induction of testicular damage in rodents (Gunn, et al. 1968b; Parizek, et al. 1969). Conversely, cadmium is able to prevent both the lethal and the growth retardation effects induced by toxic quantities of selenium (Hill, 1974).

Cadmium administration also causes the elevation of a number of enzymes (hepatic pyruvate carboxylase, phosphoenol-pyruvate carboxykinase, fructose 1,6-disphosphatase and glucose 6-phosphatase), increases the concentrations of hepatic cyclic adenosine monophosphate and blood glucose while simultaneously reducing serum insulin. The administration of selenium prevents the elevation of the cadmium hepatic gluconeogenic enzymes and ameliorates the hyperglycemia, hypoinsulinemia, and glucose intolerance. Selenium does not, however, alter the cadmium induced elevation of hepatic cyclic AMP levels (Merali and Singhal, 1975). Selenium causes an increase in the biliary excretion of cadmium (Stowe, 1976). This contrasts with zinc which causes a significant reduction of biliary cadmium excretion. The mechanisms involved in the protection by selenium against cadmium toxicity have been investigated by Chen, et al. (1975) and appear to be the result of cadmium diversion by selenium from low-molecular weight proteins to less critical higher molecular weight moieties. Both selenium and cadmium are equally bound in a 1:1 ratio in plasma protein fractions ranging in size from 130,000 to 420,000 daltons (Gasiewicz and Smith, 1976).

The number of complex interactions with various metals and nutrients suggests strongly that certain sectors of the public will in all likelihood be at greater risk from cadmium than the community as a whole. For example, cadmium may pose an increased hazard to those with anemia or for those in need of additional calcium, such as pregnant women or growing children. Cadmium may be more toxic for those living in areas where zinc deficiency is common, i.e., Egypt, Iran, etc. and where protein deficiency states such as Kwashiorkor are common, i.e., many "third-world" countries. Studies of these and other sensitive groups are only now beginning.

Teratogenicity

Relatively low doses of parenterally administered cadmium have been shown to have profound effects upon the reproductive abilities of various species of experimental rodents.

Parizek and Zahor (1956) first noted in rats that a single small dose of cadmium chloride (2 mg/kg) given subcutaneously results in testicular hemorrhage and complete testicular necrosis. Subsequently, a similar effect was noted in rabbits, hamsters, guinea pigs and mice (Parizek, 1957; Meek, 1959). This effect is mediated by selective damage to the internal spermatic artery and pampiniform venous plexus rather than by a direct effect on testicular tissue (Gunn, et al. 1963b). This renders the animal permanently sterile (Parizek, 1960). Following necrosis the majority of the seminiferous tubules remain atrophic and only a few contain germinal epithelium. The Leydig cell component of the testis regenerates sporadically throughout the tissue resulting in both hyperplastic nodules and Leydig cell tumors of variable histologic appearance. These tumors exhibit a moderate degree of pleomorphism and occasional mitotic figures (Roe, et al. 1964). There is no difference in testicle size between cadmium treated mice and controls, but the seminal vesicles and other accessory sex organs decrease in size implying a decreased secretory capacity of testosterone from the damaged Leydig cells (Nordberg, 1975). This effect is prevented by the simultaneous administration of zinc with cadmium (Gunn, et al. 1963a,b). It should be pointed out that this effect is not seen in certain inbred strains of mice (Gunn, et al. 1965; Lucis and Lucis, 1969) and apparently identical Leydig cell tumors (interstitial cell tumors) are caused in rodents by a variety of other agents besides cadmium, i.e., estrogenic substances (Andarvont, et al. 1957), implanted testicular fragments (Biskind and Biskind, 1945), minor testicular trauma (Malcolm, 1972), and ligation of the internal spermatic artery and vas deferens (Fels and Bur, 1958). Testicular necrosis and subsequent interstitial cell tumor formation due to cadmium apparently have not been observed in man. Necropsy and subsequent histologic examination of the testis in fatal cases of cadmium poisoning have revealed no abnormalities despite the passage of some days or years following exposure before death (Beton, et al. 1966; Blejer, et al. 1971; Smith, et al. 1960).

Somewhat analogous effects have been observed in female rodents. Cadmium damages the ovaries of nonovulating rats in persistent estrus and in prepubertal females (Parizek, et al. 1968; Kar, et al. 1959). The lactating mammary gland is also affected by cadmium and important changes occur in the form of acinar necrosis, intralobular hyperemia, and interestitial edema. The effects on both ovary and mammary gland are prevented by the simultaneous administration of selenium (Parizek, 1968; Parizek, et al. 1968). Rats in late pregnancy are apparently more sensitive to cadmium than nongravid animals or those immediately post-partum. A single dose of 2-3 mg/kg of body weight given during the last 4 days of pregnancy results in a high mortality (76 percent) within 1 to 4 days of injection. On autopsy generalized visceral congestion, pleural effusion, enlarged kidneys, adrenal hemorrhage, and pulmonary thrombosis are prominent findings. No similar changes were seen in nonpregnant or immediately postpartum animals (Parizek, 1965).

In the pregnant rat, cadmium results in a complete destruction of the fetal portions of the placenta and death of the fetuses (Parizek, 1964). In mice, of differing strains, embryos and fetuses show a wide range of sensitivity to cadmium induced embryotoxicity and death. Crosses between resistant and sensitive strains indicate an inherited pattern of sensitivity, with cadmium crossing the placenta in both strains, but less well in the more resistant animals (Wolkowski, 1976). Rodents have a hemochorial placenta and it is unknown whether higher species would be affected in a similar manner.

Schroeder and Mitchener (1971) have carried out three generation rodent studies with a number of trace elements. Cadmium in drinking water (10 ppm) resulted in "loss of the strain." In the F_1 generation 39 young deaths occurred and 25 runts were noted compared with none in the controls. In the F_2 there were two dead litters, 48 young deaths, three failures to breed and nine runts. Again, both runting and young deaths were statistically significantly increased. A congenital abnormality, sharp angulation of the distal third of the tail was seen in 16.1 percent of live offspring. Because of breeding failures the experiment was terminated after the F_2 generation. In contrast, Suter (1975) found no detectable fertility effects, except superovulation and larger than normal litters, in inbred mouse strains injected with 1 or 2 mg/kg of cadmium chloride. Doses of 3 and 4 mg/kg resulted in a very high immediate mortality rate. Dixon, et al. (1976) found no reproductive effects in rats supplied with drinking water containing 0.1 ppm for 90 days.

While cadmium crosses the placental barrier quite poorly some passage definitely occurs. In rats this has been shown to be dose-dependent and to increase with gestational age (Sonawane, et al. 1975). In the hamster, significant amounts of cadmium cross the placenta and enter the embryo by the 8th day of gestation, the time frame corresponding to the teratogenic effects seen in the species. Zinc can prevent these effects, but does not prevent the placental transfer of radioactive cadmium (Ferm, et al. 1969).

When cadmium is administered to pregnant hamsters on days 12-14, marked effects have been noted in the facial development of the offspring. Effects include unilateral and bilateral clefts of the palate, midline clefts through the nose, thyroglossal clefts, and anophthalmia (Ferm and Carpenter, 1967; Ferm, 1967). Mulvihill, et al. (1970) have suggested that this failure of fusion is due to a mesodermal deficiency rather than to delays in shelf transportation. Selenium has been shown to have a markedly protective effect against cadmium teratogenesis in the hamster (Holnberg and Ferm, 1969). Similarly, cadmium administered to rats on gestation days 13-16 produced a dose related increase in anomalies, including micrognathia, cleft palate, clubfoot, and small lungs (Chernoff, 1973). In addition, the lung/body weight ratio was reduced indicating a specific retardation and not merely a reflection of differential organ growth rates and overall growth retardation. A single intravenous dose of 1.25 mg cadmium/kg body weight given between the 8th and 15th days of gestation produces more than 90 percent fetal deformities in rats (Samarawickrama and Webb, 1978). The most common anomaly was hydrocephalus with an incidence of 80 percent when the cadmium was given on day 10 of gestation. The mechanism of action of cadmium in producing teratologic effects, i.e., directly upon differentiating embryonic tissue or indirectly via effects on maternal tissues, remains unknown. However, it has been shown that low levels of cadmium which do not affect cellular growth can alter RNA metabolism in Chinese hamster ovary cells to a significant extent and it has been postulated that this may modify normal cell development and serve as a possible basis for teratogenic effects (Enger, 1976). The possibility of human teratogenicity has not been systematically examined and only one report (Tsvetkova, 1970) suggests such an effect. In this brief report children of women occupationally exposed to cadmium were found to have lower birth weights than 20 control infants. In view of the many factors which may contribute to lowered birth weight, i.e., parity, maternal weight, chronic maternal illness, socioeconomic conditions, maternal smoking, prenatal nutrition, etc., little credence can be placed on this report.

Mutagenicity

In the past decade cadmium has been studied in a variety of *in vitro* and *in vivo* test systems with somewhat conflicting results. Sunderman (1978) has recently reviewed *in vitro* experiments that may be relevant to metal carcinogenesis. The Environmental Protection Agency's Carcinogen Assessment Group has performed a similar review of these tests (U.S. EPA, 1977).

Cadmium has been reported to cause chromosomal or mitotic aberrations in mammalian tissue culture cell lines. These are summarized in Table 3. The majority of these studies suggest a cadmium effect. In addition, several *in vitro* studies in biochemical systems have now been reported.

Sirover and Loeb (1976) have studied 31 metal compounds *in vitro* using a system designed to detect infidelity of DNA synthesis. Both cadmium acetate and cadmium chloride demonstrated decreased fidelity, i.e., increased error frequency. Decreased fidelity of DNA synthesis *in vitro* has also been reported by Hoffman and Niyogi (1977) for cadmium, lead, cobalt, copper, and manganese.

TABLE 3

Experiments in Tissue Culture Systems Using Cadmium

Authors	Cell Culture		Observations
Zasukhina, et al. (1975)	Rat embryo	+	Chromosomal aberrations
Rohr and Bauchinger (1976)	Chinese hamster fibroblasts	+	Chromatid aberrations
Casto, et al. (1976)	Hamster embryo	+ -	Persistent morphologic alternations; enhanced transformation by simian adenovirus 7; 8-azaguanine resistance unscheduled DNA synthesis
Shiraishi, et al. (1972)	Human leukocytes	+	Chromatid breaks, dicentric chromosomes
Paton and Allison (1972)	Human leukocytes and fibroblasts	-	

These investigators also found that these metals stimulated chain initiation of RNA synthesis at concentrations that inhibited overall RNA synthesis. Murray and Flessel (1976) have reported that in vitro addition of cadmium and manganese ions to solutions of synthetic polynucleotides caused pairing of noncomplementary nucleotides and have emphasized that direct metal-nucleic acid interactions may be responsible for neoplastic transformation by metals. Zinc and magnesium did not show this effect.

Friedman and Staub (1976) have studied cadmium and numerous other compounds to determine if mutagenic substances modify DNA replicative activity. In their assay the uptake into mouse testicular DNA of (^{3}H) thymidine is measured 3.5 hours after injection of the test compound. Cadmium treated (10 mg/kg) mice showed a significant decrease ($p<.05$) in (^{3}H) thymidine uptake in comparison to control animals. The effect was, however, much less than the inhibition caused by 3-methylcholanthrene and diethylnitrosamine. This inhibitory effect may be due to cadmium's ability to impair testicular blood supply and cause complete necrosis of the testis. The dose given was at least 3-fold that required to induce this acute effect.

The results with cadmium in various microbial systems designed to detect mutations have shown quite mixed results (Table 4). McCann, et al. (1975) have reported that three of four metal carcinogens tested in the standard Ames test have been negative. They do not name these metals, but suggest that the system is not favorable for bacterial absorption of metals because of the large amount of Mg salts, citrate, and phosphate in the minimal medium.

TABLE 4

Mutagenesis Studies of Microbial Systems Using Cadmium

Author	Organism	Result
Nishioka (1975)	*B. subtilis*	+ Weak response ($CdCl_2$) - $Cd(NO_3)_2$
Takahashi (1972)	*S. cerevisiae*	+ Reported in CAG Assessment
Sunderman (1978)	*S. typhimurium*	- Two independent investigators reported to Sunderman

A fairly large number of studies now exist which have examined a variety of mammalian cells for cytogenetic abnormalities following exposure of the intact animal or man to cadmium (Table 6). Again mixed results have been obtained. It should not be forgotten that most of the studies on workers reflect a mixed exposure to zinc and lead, in addition to cadmium. Since smelters also commonly process relatively crude materials exposure to other metals such as chromium, arsenic, nickel, etc. cannot be eliminated as possible contributors to the observed effects. Synergistic effects between metals may also confuse the results from such studies.

Table 6 lists several studies dealing with point mutation. Drosophilia studies have been negative to date (Table 6) as have dominant lethal tests in mice (Table 5).

Although some of the above cited studies demonstrate mutagenic activity, at this point in time the relationship between a substance's mutagenic activity in lower forms and its potential as a human carcinogen is still not clear. Correlations between mutagenicity and carcinogenesis are quite good for certain classes of compounds and relatively poor for others. A major problem is that relatively few substances are recognized as unequivocal carcinogens for man. Chromosomal aberrations have now been noted in human leucocytes in response to a wide variety of diverse substances. The ultimate significance in terms of human health remains to be elucidated.

Carcinogenicity

This particular aspect of cadmium toxicology has received a number of recent reviews (International Agency for Research on

TABLE 5

Chromosome Mutation Studies on Mammalian Cells Exposed *In Vivo*

Author	Cells		Result and Comment
Shiraishi and Yosida (1972)	Human leucocytes from Itai-Itai Patients	+	Increased chromatid breaks, isochromated breaks, chromatid translocations, dicentrics, and acentric fragments
Doyle, et. al. (1974)	Sheep leukocytes	+	Reported in CAG Assessment
Shimada, et. al. (1976)	Mouse cocytes	+	Reported in CAG Assessment
Deknudt and Leonard (1976)	Human leucocytes from exposed workers	+	Chromatid aberrations and chromosome anomalies. Similar rate of effect in both high and low exposure groups. Chromatid breaks exchanges.
Bauchinger, et al. (1976)	Human leucocytes from exposed workers	+	Mixed metal exposure. (including Cd)
Bui, et al. (1975)	Human leucocytes	-	Swedish battery workers
		-	Itai-Itai patients
Gilliavod and Leonard (1975)	Dominant lethal test in mice	-	
	Mouse spermatocytes	-	No translocations.
	Mouse F_1 translocation test	-	
Epstein, et al. (1972)	Mouse dominant lethal	-	

TABLE 5 (Continued)

Author	Cells		Result and Comment
Leonard, et al.(1975)	Bovine leucocytes	-	Heavy mixed metal exposure (Cadmium 50 x control levels) Exposure fatal to 6 of 15 animals.
Deknudt, et al. (1973)	Human leucocytes	+	Mixed metal exposure (including Cd)
Suter (1975)	Dominant lethal test in female mice	-	Actual increase in living implants. No increase in dead implants.

TABLE 6

Point Mutation Studies with Cadmium

Author	Organism	Result
Shabalina (1968)	Drosophilia	-
Friberg, et al. (1974)	Drosophilia	-
U.S. EPA (1977)	Saccharomyces	+

Cancer (IARC) Monographs, 1973, 1976; U.S. EPA, 1977; NIOSH, 1976; Sunderman, 1977, 1978; Hernberg, 1977).

Animal studies have amply shown that the injection of cadmium metal or salts causes malignancies (sarcoma) at the site of injection and testicular tumors (Leydig cell interstitial cell). These studies are summarized in Table 7.

Injection site sarcomas arise from either subcutaneous or intramuscular administration. In comparison with other similar sarcomas in rodents they appear to be well differentiated (Heath, 1962), but give rise to distant metastases and may be permanently transplanted (Heath and Webb, 1967). There is now general agreement that studies demonstrating the production of sarcomas in rodents at the site of injection are not germane to cancer in man. A large number of chemical irritants and physical agents are known to cause sarcomas in rodents and they should not be considered as acceptable evidence of carcinogenicity for the human, except perhaps by the injection route.

Leydig cell (interstitial cell) tumor formation was briefly considered in a previous section of this evaluation. These tumors develop in rodents many months following the complete necrosis of the testis. Cadmium is only one agent producing this effect in rodents, supra vide. Interstitial tumors do not differ morphologically irrespective of their mode of origin although those induced by cadmium exhibit more androgenic activity than those resulting from total vascular ligation (Gunn, et al. 1965). Histologically, the tumors are well-differentiated and composed of Leydig cells of relatively uniform appearance (Reddy, et al. 1973) and retain their

TABLE 7

Animal Tumorogenesis Induced by Cadmium Injection

Authors	Species	Compound	Route	Tumor and Incidence
Haddow, et al. 1961	Rats	Cd containing ferritin	s.c.	Sarcomas (35%) Interstitial cell tumors
Heath, 1962	Rats	Cd powder	i.m.	Sarcomas (75%)
Heath and Daniel, 1964	Rats	Cd powder	i.m.	Sarcomas (90% and 75%
Kazantzis, 1963	Rats	CdS	s.c.	Sarcomas (60%)
Kazantzis and Hanbury, 1966	Rats Rats	CdS CdO	s.c. s.c.	Sarcomas (60%) Sarcomas (80%)
Haddow, et al. 1964	Rats	$CdSO_4$	s.c.	Sarcomas (70%)
Roe, et al. 1964	Rats	$CdSO_4$	s.c.	Interstitial cell tumors (55%)
Gunn, et al. 1963a	Mice	$CdCl_2$	s.c.	Interstitial cell tumors (77%)
	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (68%)
Gunn, et al. 1964	Rats	$CdCl_2$	s.c.	Sarcomas (41%)
	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (86%)

TABLE 7 (continued)

Authors	Species	Compound	Route	Tumor and Incidence
Gunn, et al. 1967	Rats	$CdCl_2$	s.c.	Sarcomas (10%)
Knorre, 1970	Rats	$CdCl_2$	s.c.	Sacromas (13%)
Knorre, 1971	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (40%)
Lucis, et al. 1972	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (87%) Sarcomas (13%)
Reddy, et al. 1973	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (80%)
Furst and Cassetta, 1972	Rats	Cd powder	i.m.	Sarcomas (54%)
Favino, et al. 1968	Rats	$CdCl_2$	s.c.	Interstitial cell tumors (100%)
Malcolm, 1972	Rats	$CdCl_2$	s.c.	Sarcomas (?) Interstitial cell tumors (?)

steroidogenic characteristics. These tumors are androgenically functional (Gunn, et al. 1965; Favino, et al. 1968), although producing less testosterone than normal. The malignant potential of interstitial cell tumors is problematical: "The dividing line between hyperplasia and neoplasia is as indefinite as the rats studied and an even greater problem and one of vital concern in prognosis, is the distinction between benign and malignant tumors. At present, probably the only reliable criterion of malignancy is the presence of metastases" (Roe, et al. 1964). Cadmium induced interstitial tumors have never been reported to metastasize. The spontaneous development of interstitial cell tumors in rats varies considerably with the strain. Aged Fischer rats have been shown to have a very high rate (68 percent) of spontaneous interstitial cell tumor formation (Jacobs and Huseby, 1967). Malcolm (1972) has noted the development of these tumors in control animals from the weekly palpation during examination. Interstitial tumors of the testis are rare in man and account for less than 2 percent of all testicular tumors (Dixon and Moore, 1953). Out of a total of 49 cases reported in the literature only five were reported as being malignant. None of the 12 cases in the Army series, followed from 4 to 16 years had evidence of metastases or recurrence (Dixon and Moore, 1953). This tumor has yet to be reported in association with human exposure to cadmium.

In general, the simultaneous administration of zinc is protective against the formation of either sarcoma and/or interstitial cell tumor development (Gunn, et al. 1963b, 1964). However, zinc powder given intramuscularly fails to prevent formation when the inducing agent is cadmium powder (Furst and Cassetta, 1972).

Several long term feeding and inhalation studies with cadmium have been carried out, but the induction of tumors has not been noted.

Schroeder, et al. (1964) has conducted lifetime exposure studies in Swiss mice. The animals were supplied with drinking water containing 5 ppm of cadmium acetate. Both males and females experienced some shortening of life span in comparison with the controls. The exposed animals had fewer tumors than the controls. Using rats at the same dosage they subsequently reported similar negative results and concluded that cadmium could not be considered carcinogenic in the doses given (Schroeder, et al. 1965).

Levy, et al. (1973) gave three groups of mice weekly doses (1.0, 2.0 and 4.0 mg/kg body weight) by gavage for 18 months. No difference between exposed and control animals was noted in regard to general health or tumor incidence at 18 months. Similar experiments with hooded CB rats using doses of 0.2, 0.4 and 0.8 mg/kg of cadmium sulphate weekly for 2 years were carried out by Levy and Clark (1975) with again no difference in tumor incidence in exposed and control groups. Decker, et al. (1958) reported on a rat study in which rats were supplied cadmium chloride in drinking water in the following concentrations: 0.1, 0.5, 2.5, 5.0, 10.0 and 50 ppm as cadmium. The highest dose group was terminated at 8 months because of appreciable stunting. Two animals from each of the other groups were sacrificed quarterly for up to 1 year. There were no differences in body weight between control animals and those receiving up to and including 10 ppm; nor were there differences in food or water intake or pathologic changes.

Anwar, et al. (1961) exposed eight dogs to 0.5 to 10 ppm cadmium (as cadmium chloride) for 4 years. Aside from a splenic nodule in a dog treated with the lowest dose, no tumors were observed.

Paterson (1947) carried out inhalation studies with cadmium oxide and cadmium chloride fume using rats. He used animals treated in the following way: 136 rats surviving the acute LD_{50} (800-1,000 min. mg/m^3); 100 rats surviving one-half the LD_{50}; and 200 rats exposed to approximately one-quarter the LD_{50} of cadmium chloride every 2 weeks for 6 months (12 exposures). Sacrifices were made periodically and the experiments were terminated 6 months after beginning exposure. No tumors were noted in the lungs. Apparently other organs were not examined.

Malcolm (1972) gave rats up to 0.2 mg of cadmium sulphate subcutaneously and up to 0.8 mg weekly by stomach tube for 2 years. In a third experiment, mice were given doses up to 0.02 mg/kg of body weight subcutaneously at weekly intervals for 2 years. Except for a few sarcomas seen in the rats given subcutaneous injections and Leydig cell tumors (also seen in the controls) these studies were negative at the time reported. Several of the above briefly described oral intake and inhalation studies have been termed inadequate (IARC, 1976), apparently on the basis of the relatively small doses employed. Schroeder's work was specifically designed to simulate human exposure and for the most part the doses given seem realistic. Obviously, the doses were well below the maximum tolerable doses usually used today in attempting to establish the carcinogenic potential of various substances. Nonetheless, there seems to be a rather large volume of negative animal data.

Koller (1978) has reported on the effect of cadmium exposure on tumor growth and cell-mediated cytotoxicity in mice inoculated with MSB-6, a MSV derived tumor cell line. A dose-dependent inhibition of tumor growth was seen in those mice receiving cadmium. At 3 and 30 ppm dose levels, no inhibition of body weight accompanied tumor growth reduction, whereas at 300 ppm, there was a small inhibition of body weight gain. Cadmium exposed animals demonstrated significantly higher levels of cell mediated tumor cytotoxicity than controls. No data on the effects of cadmium upon the growth of nonviral-induced tumors has yet appeared.

Potts (1965) was the first to draw attention to the possibility of cancer in man as a result of cadmium exposure. Previously, Friberg (1950) had noted three cases of cancer among 17 deaths in alkaline battery workers. The sites were bladder, lung, and colon. While there was no control group this would not seem an excessive number of cancer deaths, i.e., 17.6 percent. Potts reported on the causes of death of eight men with at least 10 years exposure. Five of the eight died of cancer. Their ages, years of exposure, and tumor sites are shown in Table 8.

The remaining three men died from auricular fibrillation, bronchitis, and atheroma. Potts, while recognizing that the number of cases was very limited, felt that the association between cancer in man and cadmium should be "fully explored." Normally, one would not expect more than two cancer deaths out of the eight deaths observed.

TABLE 8

Data Related to Five Deaths from Cancer*

Age	Years of Exposure	Cause of Death
75	14	Carcinoma of prostate
65	37	Carcinoma of prostate
53	35	Carcinoma of bronchus
65	38	Carcinoma of prostate
59	24	Carcinomatosis

*Source: Potts, 1965

Kipling and Waterhouse (1967) surveyed a group of 248 workers who had been exposed for a minimum period of 1 year to cadmium oxide. Twelve of these men had died and the causes of death ascertained. The twelve include the eight reported by Potts. They computed the expected number of cases by site which would have occurred by chance and compared it against the observed. Their data are shown in Table 9.

From Table 9, for cancers at sites other than the four listed, a total of 7.53 cases were expected (13.13-5.60), but only two at other sites were observed. It is unclear as to why the number of expected prostate cancers is so small, i.e., 0.58, even adjusting for age. Cancer of the prostate is very common in elderly males and at least three of the four cases (Potts' cases) were elderly, i.e., 65, 65, and 75 years. Cancer of the prostate in the United States is the third leading cause of cancer death in males aged 55-74 and the second leading cancer cause of death in males over 75. The percentage of cancer deaths due to prostate cancer for these two age groups is 7.6 and 19.3 percent, respectively. Slightly over 2 percent of all U.S. male deaths and about 10 percent of cancer deaths are from this cause. The long term incidence (death rate 13-14/100,000) trends for cancer at this site have not changed over the period 1940-1974. The death rates are similar for this site between England and Wales, 11.51/100,000, and the U.S., 13.90/100,000 (National Cancer Institute (NCI), 1977). Thus, the expected figure of Kipling and Waterhouse seems about half of that anticipated based on England's national prostate cancer statistics. It is of considerable interest that the rates for cancer of the

TABLE 9

Survey of Workers Exposed to Cadmium Oxide*

Site of Cancer	Expected	Observed	Probability of Occurrence
All sites	13.13	12	0.660
Bronchus	4.40	5	0.449
Bladder	0.51	1	0.398
Prostate	0.58	4	0.003
Testis	0.11	0	0.898

*Source: Kipling and Waterhouse, 1967

prostate in Japan, the country with by far the highest daily intake of cadmium, are the lowest for any developed country in the world, i.e., 1.93/100,000. This contrasts sharply with the rate for Sweden (18.33/100,000) which is the highest in the world. The Swedish daily intake and body burdens of cadmium are among the lowest yet reported (Kjellstrom, et al. 1978a).

Holden (1969) in a letter to the editor mentions two cancer deaths in cadmium workers (prostate, bronchus). He gives no denominator data. It seems possible that these cases were included in the previous survey by Kipling and Waterhouse.

Lemen, et al. (1976) conducted a retrospective cohort mortality study using reported causes of death among cadmium smelter workers who had achieved at least 2 years of exposure in the years 1940-1969. Ninety-two deaths were known to have occurred out of the employee cohort of 292 white males. Comparison was made between the observed number of deaths and that expected based on age, time, and cause-specific mortality rates for the total U.S. white male population. There was a slight deficit of total deaths, i.e., 92 observed v. 99.32 expected. All this deficit is accountable by the extremely low number of deaths due to heart disease; only 24 were observed and 43.52 were expected, a difference significant at the $p < 0.01$ level. Twenty-seven deaths were observed as a result of malignant neoplasms and 17.57 were expected. This is significant at the $p < .05$ level. Most of this excess was accounted for by neoplasia of the respiratory system, where 12 were observed and 5.11 expected, a difference significant at $p < 0.05$. The risk of prostatic cancer was also elevated, i.e., 4 cases observed v. 1.15

expected although this difference is not significant. When further consideration was given to the time interval since onset of exposure, a significant risk of prostate cancer was demonstrated (4 observed v. 0.88 expected, $p<0.05$) 20 years after onset of cadmium exposure. It should be pointed out that Lemen's group was exposed to arsenic, a well-documented human carcinogen, and Potts' group to nickel, another generally accepted human carcinogen. These elements may account for the increased incidence of respiratory tract tumors in the studies previously discussed. Kjellstrom, et al. (1978b) has reported preliminary mortality data for 269 cadmium-nickel battery workers and a control group of 328 alloy factory workers. Cancer deaths were not statistically different in the two groups, but the alloy factory workers were found to have an increased mortality from prostate cancer. Certainly the idea that prostatic cancer in man is somehow related to cadmium cannot be entirely discounted without careful industry wide studies.

While of questionable relevance to the human prostate cancer question, specifically designed long term rodent studies reported by Levy (1973) and Levy and Clark (1975) failed to detect evidence of prostate neoplasia.

Humperdinck (1968) followed up eight cases of chronic poisoning previously reported by Baader (1952). Four had died, one of lung cancer. Out of 536 workers with some cadmium exposure he was only able to find five cases of cancer (including the one of lung cancer) and concluded that his data did not support a causal relation between cadmium exposure and cancer.

McMichael, et al. (1976) studied the mortality of workers from four rubber producing plants. The standard mortality rate (SMR) was 94 for the full cohort. The SMRs for all cancer sites was not elevated, but at some specific sites an increase was noted: stomach, 148; rectum, 116; prostate, 119; all leukemia, 130; lymphatic leukemia, 158; and lymphosarcoma-Hodgkin's disease, 129. Rubber plant workers are exposed to a great number of compounds including benzene, an accepted human carcinogen. The relationship of these tumors to cadmium is highly problematical.

Kolonel (1972, 1976) has suggested that there may be an association between cadmium and renal cancer. He examined the incidence of cancer at several sites for persons with an inferred occupational history of cadmium exposure and in a control population. Cadmium exposure was based solely on job classification information provided by patients on admission to a cancer research hospital. The only significant association was with renal cancer. He had expected to find an increased incidence of prostatic cancer, but none was detected. To help substantiate and refine the association he noted a 4-fold increase in renal cancer among smokers with an occupation suggesting cadmium exposure in comparison to controls. Tobacco, as previously mentioned, contains appreciable amounts of cadmium. However, nonsmoking, cadmium exposed workers actually were found to have less renal cancer than controls. This suggests that some other agent in tobacco smoke may be responsible, or that at most, smoking operates in some synergistic manner with cadmium. Obviously this is an extremely tenuous association. Among all the tumor sites specifically reported for cadmium workers, many of whom probably were smokers, the kidney has yet to be mentioned.

In summary, the available epidemiologic evidence does not suggest that cadmium can be definitely implicated as a human carcinogen.

CRITERION FORMULATION

Existing Guidelines and Standards

Numerous domestic official agencies, foreign governments, and private parties have suggested standards or limits for cadmium in various environmental media. The more germane of these are presented in Table 10.

Current Levels of Exposure

The exposure section of this document deals with general environmental exposure to cadmium. Food represents the major route of human exposure, with air contributing only a negligible amount to the total intake, except in tobacco smokers. Drinking water normally would account for less than 10 percent of the daily total absorption for the vast majority of the population. Percutaneous absorption is inconsequential.

It is recognized that approximately 100,000 Americans have potential occupational exposure to cadmium (NIOSH, 1976). The spectrum of occupational exposure varies from negligible to those situations producing acute and/or chronic toxicity and even death. While efforts are being made by those in occupational health to reduce exposure to a minimum and eliminate adverse health effects it must be recognized that no general environmental standard can prevent damage from overexposure in the occupational setting.

Special Groups at Risk

Persons with severe nutritional deficiency, i.e., calcium, zinc, protein, Vitamin C and D, etc., which may be aggravated by cadmium are conceivably at special risk, although human data

TABLE 10

Regulatory Standards, Limits, or Criteria for Human Health Protection

Source	Media Air (Inhalation)	 Water (Ingestion)	 Food (Ingestion) Entity
Occupational Safety and Health Administration (OSHA) (1974) (39 (125) FR 23543)	100 $\mu g/m^3$[1]		
NIOSH (1976)	40 $\mu g/m^3$		
U.S. EPA (1975b)		10 $\mu g/l$	
FDA (1978) (21 CFR 109.4, 509.4)			0.5 $\mu g/ml$[2]
WHO (1971)		10 $\mu g/l$	
American Conference of Governmental Hygenists (ACGIH) (1977)	50 $\mu g/m^3$		
Multimedia Environmental Goals for Environmental Assessment (1977)	0.12 $\mu g/m^3$	WH1-1.9 $\mu g/l$[3] WH2-0.7 $\mu g/l$[4]	
NAS (1972)		10 $\mu g/l$	
USSR (suggested)[5]		1 $\mu g/l$	
CANADA (1969)		10 $\mu g/l$	
OHIO[6]		5 $\mu g/l$(streams)	

1. For cadmium fume. Limit for cadmium dust is 200 $\mu g/m^3$
2. Based on ceramic pottery and enamelware leaching solution test

3,4. EPC (estimated permissible concentration) WH1 is derived from the assumption that the maximum daily safe dosage results from 24-hour exposure to air containing the estimated permissible concentration in air, assuming 100 percent absorption and that the same dose is therefore permissible in the volume of water comsumed per day; WH2 is the estimated permissible concentration of the substance in water based on considerations of the safe maximum body concentration and the biological half-life of the substance

5. Krasovskii, G.N., et al. 1976
6. Lykins, B.W.,Jr. and J.M. Smith, 1976

concerning these effects are presently scant. Such a risk is obviously additive since these deficiences can in and of themselves be sufficient to cause disability and/or fatal disease. Obviously, persons in such precarious physiologic balance are particularly vulnerable to a wide variety of biologic and chemical hazards.

Some persons with diets that are adequate in terms of vital nutrients, calories, etc., but who subsist on otherwise skewed diets such as vegetarians or those eating unusual quantities of visceral meats, fish, or seafoods, which can contain rather large amounts of cadmium, may also be at increased risk. The additional risk to such population groups posed by an additional exposure increment from ambient cadmium remains to be assessed.

Basis and Derivation of Criteria

There is no doubt that cadmium is a teratogen in several rodent species when given in large parenteral doses. Doses of this magnitude (4-12 mg/kg) would surely produce severe, if not fatal toxic symptoms in man. In the human only small amounts of cadmium cross the placental barrier (Lauwerys, et al. 1978). Only one report, from Russia (Tsvetkova, 1970), suggests any effect, i.e., low birth weight and "several children with rickets or dental trouble." Details are lacking in this report and it should not be construed as implicating cadmium without further data.

The studies of whether cadmium is mutagenic are inconsistent. The reports of chromosomal aberrations in both itai-itai patients and cadmium workers are conflicting. Dominant lethal studies have been negative as are tests for spermatocytic chromosome aberrations in male mice and their first-generation offspring (Gilliavod and

Leonard, 1975). Studies of mutagenic activity in nonmammalian life forms have given inconsistent results.

There is no question that the injection of cadmium into rodents results in injection-site sarcomas and interstitial cell tumors of the testis. Sarcoma production in rats is a common sequela to the injection of irritants and could be regarded as a nonspecific response to fibroblast injury. Interstitial tumors appear to result from the hyperplasia and metaplasia of tissue regeneration following vascular-mediated testicular damage. There is no evidence that these tumors are malignant neoplasms; however, this does not refute the tumorogenic potential of cadmium.

The human evidence for the carcinogenicity of cadmium is conjectural, based on very small numbers, and confounded by exposures to other elements which are known to be human carcinogens. The reports on British battery workers and the work of Lemen, et al. (1976) suggest an increase in prostrate and lung cancer. These men were also exposed to nickel and/or arsenic, but in amounts of one hundred to two hundred times less of cadmium exposure level. Kolonel's (1972, 1976) work confirmed neither of these sites, but suggested an association with renal cancer. This work is inadequate in that it assumes an exposure to cadmium based upon an occupational questionnaire. There have been no case reports of renal cancer in known cadmium-exposed workers. Cigarette smoking would appear to have a firmer association with renal neoplasia, rather than cadmium. The geographic distribution of prostrate cancer (Japan, Sweden, USA) suggests that an inverse relationship exists to cadmium exposure. From the known mortality study data cited it might be argued that cadmium exposure reduces general mortality or is a potent protective factor against cardiovascular disease. The case for cadmium as a carcinogen is not persuasive when the existing data are critically reviewed, but it has been viewed by some as suggestive from the public health perspective.

It is not recommended that cadmium be considered a suspect human carcinogen for purposes of calculating a water quality criterion. However, the weight of evidence for oncogenic potential of cadmium is sufficient to be "qualitatively suggestive" and is not to be ignored from a public health point of view. The EPA Carcinogen Assessment Group has reviewed cadmium and their summary is included in the Appendices of this document.

The criterion is based on established health effects. The data implicating cadmium as a cause of emphysema and renal tubular proteinuria is firmly established. Emphysema has been reported only after airborne exposures and has been documented for both man and animals. It would seem to result from a direct effect upon lung tissue of which cadmium salts are known irritants.

There is evidence from occupational studies that the kidney is more sensitive to the effects of cadmium than the lung. In exposed workers proteinuria occurs in higher incidence and in a shorter time period than emphysema. It seems entirely justified to conclude that the kidney is the critical target organ.

It is generally accepted that the critical cadmium level at which renal dysfunction occurs is approximately 200 µg/g wet weight of renal cortex. Autopsy studies indicate that at present the average kidney concentration in nonsmokers is approximately onetwelfth this level. In smokers the concentration is about twice as high, i.e. 30-39 µg/g.

Friberg, et al. (1974) has estimated that the critical level is reached at daily ingestion levels of 250-350 µg per day over 50 years. Since the average, nonoccupationally exposed American probably does not have an intake from all sources exceeding 25-50 µg/d there would again seem to be a reasonable "safety-factor" of 5 to 12 in existence. While this is not the comfortable margin or many orders of magnitude usually recommended by toxicologists it should provide a margin of "safety" to the general public for the foreseeable future.

NIOSH (1976) recommends that workers should not be exposed to airborne cadmium at a concentration greater than 40 $\mu g/m^3$ as a time weighted exposure for up to a 40 hour work week. This standard is designed to protect the health and safety of workers over an entire working life time. Compliance should prevent adverse effects on the health of the worker. Several studies have indicated no adverse effects at levels of 31 and 16-29 $\mu g/m^3$ (Lauwerys, et al. 1974; Tsuchiya, et al. 1976). Effects of renal function (proteinuria) and a reduction in mean pulmonary function have been noted at levels of 66 $\mu g/m^3$ cadmium dust (21 $\mu g/m^3$ respirable dust; < 5 µm) although some of these workers probably had experienced exposure, at least intermittently, to cadmium dust at higher, but unknown, concentrations. A limit of 20 $\mu g/m^3$ respirable dust offers a greater, and "probably sufficient margin of safety" in comparison with the 50 $\mu g/m^3$ recommended by ACGIH (1977) and Lauwerys, et al. (1974).

From the figure 20 µg/m^3 it can be calculated that a worker might absorb about 500 µg during a work week, i.e., 20 µg/m^3 respirable particle (anything less than 5 microns mean average diameter) x $10m^3$ inhaled/day x 5 days x 0.5 (lung absorption rate). This is approximately 143 µg/day intake and 72 µg/day absorbed. To this intake the average daily intake from food and general environmental sources can be added, i.e., 10-50 µg (5 percent absorption). This suggests that an exposed worker may have an approximate intake of 150 µg/d or 75 µg/d absorbed and still be safe. However, a healthy worker may not be representative of the American population as a whole.

From Japanese dietary intake data where itai-itai disease is prevalent, and studies on the age-specific incidence of proteinuria, it may be possible to estimate a lowest observed effect level for ingested cadmium. In areas where itai-itai disease is most common, about 85 percent of the daily cadmium intake is derived from rice, the locally grown grain staple (Muramatsu, 1974). Nogawa, et al. (1978) have shown that the prevalence of tubular proteinuria, as measured by retinol binding protein excretion, in persons under age 70 does not begin to rise above that seen in control populations until the cadmium levels in rice exceed 0.40-0.49 µg/gm. The Japanese diet in the area of endemic itai-itai disease and even in the homes of patients with the disease are precisely known (Friberg, et al. 1974). Approximately 2,100 calories are consumed daily, with carbohydrate accounting for about 1,725 calories daily, which is equivalent to the ingestion of 430 gm/d. The lowest observed effect level for Japanese can be calculated as follows:

$$\frac{430\ \text{gm/d} \times 0.45\ \mu\text{g/gm (rice)}}{0.85} = 228\ \mu\text{g/day}$$

This Japanese figure is slightly below the estimate of 250 µg/day given by Friberg, et al. (1974) as an effect level. The lowest observed effect level for a Western European or American population with correspondingly larger body size would be expected to be somewhat greater (i.e., 301 µg/day).

Assuming 5 percent absorption, 301 µg/day ingested represents 15 µg/day absorbed. Approaching the problem of estimating minimal effect input using inhalation data yields only somewhat higher minimal effect input. From the data of Lauwreys, et al. (1974):

$$21\ \mu\text{g/m}^3 \times 10\ \text{m}^3 \times 0.25 \times \frac{5}{7} = 37.5\ \mu\text{g/day}$$

In the above, lung retention is assumed to be 25 percent and workers are assumed to inhale 21 µg/m^3 five days per week.

The Working Group of Experts for the Commission of European Communities has estimated (Comm. Eur. Communities, 1978) that the threshold effect level of cadmium by ingestion is around 200 ug daily corresponding to an actual absorption of 12 µg/day. For smokers this estimate is reduced by about 1.9 µg to 10.1 µg which corresponds to an oral intake of 169 µg. Using a second approach based on metabolic modeling of the above type, this same group derived a threshold effect level of 248 µg daily when pulmonary absorption is negligible.

Using the data presented in this and preceeding sections of the document, it is possible to construct several exposure scenarios encompassing possible best-to-worse case exposure situations that might be domestically encountered as seen in Table 11.

From these scenarios it can be calculated that ingested water contributes relatively little to the daily retained cadmium entering the body i.e., 0.53, 5.1, and 7.6 percent respectively for the worst, average, and best cases. Water could become a significant contributor to overall cadmium intake and retention only if the secenarios are reconstructed by substituting the worst case water data for that in the average and best cases. However, even in the very unlikely event that such situations occur the total cadmium intake and retention remain comparatively modest, i.e., 53.6 µg/d intake and 4.4 µg/d retained in the average case. The totals for the best case substitution are substantially less, i.e., 32.02 µg/d intake and 2.605 µg/d retention. Therefore, it may be concluded that there are no circumstances in which ambient waters meeting current drinking water standards pose a threat to human health.

Based on the foregoing data and discussion it seems entirely justifiable to conclude that water constitutes only a relatively minor portion of man's daily cadmium intake. From the above analysis it is obvious (average case scenario) that drinking water contributes substantially less to human cadmium intake and/or retention than smoking a package of cigarettes daily. From this analysis it appears that a water criterion needs to be no more stringent than the existing primary drinking water standard (10 µg/l) to provide ample protection of human health.

TABLE 11

Worst Case - Maximally Exposed Persons

Exposure Sources	Exposure	Cd Intake/d	Absorption Factor[+]	Cd Retention/d
Air-Occupational	0.1 mg/m^3*	714 μg	0.5	357.0 μg
Air-Ambient	0.4 μg/m^3	8 μg	0.5	4.0 μg
Air-Smoking (three packs)	3.0 μg/pack	9 μg	0.5	4.5 μg
Foods	-----	75 μg**	0.1	7.5 μg
Drinking Water	10 μg/l***	20 μg	0.1	2.0 μg
		826 μg		375.0 μg

* OSHA Standard for Cadmium fume (OSHA, 1974. 39 (125) FR 23543).

** Pahren and Kowal, 1978. Less than 1 percent of diets are expected to exceed this value.

*** See Exposure Section. Less than one water supply in 300 exceeds this value.

+ These absorption factors may be considered maximal for man.

Average Case

Exposure Sources	Exposure*	Cd Intake/d	Absorption Factor[+]	Cd Retention/d
Air-Ambient	0.03 μg/m^3	0.6 μg	0.25	0.15 μg
Air-Smoking (one pack)	3.0 μg/pack	3.0 μg	0.25	0.75 μg
Food	-----	30.0 μg	0.05	1.50 μg
Drinking Water	1.3 μg/l**	2.6 μg	0.05	0.13 μg
		36.2 μg		2.53 μg

* Average for both sexes excluding drinking water (Exposure Section).

** See Exposure Section. Average cadmium concentration in a survey of 969 U.S. Community Water Supply Systems (McCabe, et al. 1970).

+ These absorption factors are considered to be the most realistic available.

TABLE 11 (continued)

Best Case - Minimally Exposed Persons

Exposure Sources	Exposure	Cd Intake/d	Absorption Factor	Cd Retention/d
Air-Ambient	0.001 µg/m^3	0.02 µg	0.25	0.005 µg
Food	-----	12.00 µg	0.05	0.600 µg
Water	0.5 µg/1*	1.00 µg	0.05	0.050 µg
		13.02 µg		0.655 µg

* McCabe, 1974. This data indicates that 37 percent of community water supplies had less than 1.0 µg Cd/1, which was the practical limit of analytic sensitivity at the time of his survey.

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APPENDIX I

Summary and Conclusions Regarding The Carcinogenicity of Cadmium

A water quality criterion for cadmium based on epidemiology studies of workers exposed to cadmium dust is included here for reference, even though the Agency recommends that the criterion based on renal toxicity be used. The reason for this inclusion is that the evidence is suggestive, but not conclusive, that inhaled cadmium induces prostate cancer and that ingested cadmium that is systemically absorbed is expected to induce the same response as inhaled cadmium.

Environmental exposure to cadmium occurs by several routes. The estimated cadmium retention of an individual from food is about 3.0 µg/day; water, 0.09 µg/day; and air, 0.15 µg/day. People smoking five cigarettes per day have an additional retention of about 0.35 µg cadmium. The production of refined cadmium metal is a potential source of cadmium for local surface water. In drinking water the average level of cadmium is on the order of 1 µg/l, but may be as high as 10 µg/l.

Cadmium has been reported to cause chromosomal or mitotic aberrations in mammalian cell culture lines. *In vitro*, it induces cellular transformation and also enhances transformation of virus-infected mammalian cells. These tests are known to be highly correlated with oncogenicity. Further it has been shown to produce adverse effects in both man and experimental animals, e.g., pulmonary emphysema and renal tubular damage. In human tissues, the concentration of cadmium increases up to the age of 50 years.

There is suggestive evidence from four occupational studies of highly-exposed workers that inhalation of cadmium may be associated with prostrate cancer in humans. Subcutaneous injection of soluble cadmium salts in both rats and mice caused interstitial cell tumors of the testis. However, orally-administered cadmium has failed to induce carcinogenic responses in rats and mice, perhaps because it is not absorbed readily from the gastro-intestinal tract.

It is, therefore, possible that cadmium in drinking water and fish could induce prostate cancer in humans. A water quality criterion based on lifetime risk of 10^{-5} is calculated using the data of Potts, (1965) for proportional mortality in alkaline battery factory workers with the assumption of a 50 percent absorption for inhaled cadmium, 10 percent absorption for ingested cadmium, a fish bioconcentration factor of 64.0, and other assumptions common to the water quality risk assessments. The result is that the water concentration should be less than 0.28 micrograms per liter in order to keep the lifetime risk below 10^{-5}.

Quantitative Risk Estimates for Carcinogenicity of Cadmium (Cd)

From the CAG document (U.S. EPA, 1978), the lifetime risk to atmospheric Cd is $R=(1.879)\ (10^{-3})\ (X)$, where X is the lifetime average daily air concentration in $\mu g/m^3$.

The Cd intake from a concentration of 1 $\mu g/m^3$ of Cd in the air is:

1 $\mu g/m^3$ x 24 $\mu g/day$ = 24 $\mu g/day$ assuming 100 percent absorption.

Studies show that 50 percent absorption may be more realistic, therefore the Cd intake is:

$$24\ \mu g/day \times 0.5 = 12\ \mu g/day$$

If this amount of Cd were absorbed from the typical ambient water exposure pathways (assumed to be 2 liters/day of drinking water, and 0.0065 kg/day of fish products) with a fish bioconcentration factor of 64, the resulting level of Cd in ambient water, C, would be:

$$12\ \mu g/day = C_1\ (2 + (0.0065)\ (64))$$

$$4.966\ \mu g/l = C_1$$

In order to absorb this much from water and fish (assume 10 percent absorption from the GI tract), the water concentration corresponding to 1 $\mu g/m^3$ of air would have to be 49.66 $\mu g/l$. Therefore, 1 $\mu g/m^3$ in air produces a risk equivalent to a water and fish consumption resulting from 49.66 $\mu g/l$ in the water. The air level giving a lifetime risk of 10^{-5} is:

$$X_1 = 10^{-5}/(1.879 \times 10^{-3}) = 0.532 \times 10^{-2}\ \mu g/m^3$$

This corresponds to a water level of

$$C = 49.66 \times 0.532 \times 10^{-2} = 0.2642\ \mu g/l$$

$$0.26\ \mu g/l$$